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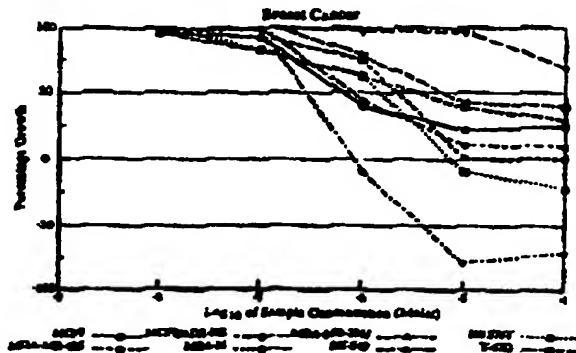
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(54) Title: DHA-PHARMACEUTICAL AGENT CONJUGATES

(57) Abstract

The invention provides conjugates of *cis*-docosahexaenoic acid and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.



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## DHA-PHARMACEUTICAL AGENT CONJUGATES

### Background of the Invention

Improving drug selectivity for target tissue is an established goal in the medical arts. In general, it is desirable to deliver a drug selectively to its target, so that dosage and, consequently, side effects can be reduced. This is particularly the case for toxic agents such as anti-cancer agents because achieving therapeutic doses effective for treating the cancer is often limited by the toxic side effects of the anti-cancer agent on normal, healthy tissue. The problems relating to lack of drug selectivity can be exemplified by Taxol®.

Taxol® (paclitaxel) was first isolated in 1971 from the bark of Taxus brevifolia and was approved in 1992 by the US Food and Drug Administration for treatment of metastatic ovarian cancer and later for breast cancer. Its mechanism of action is believed to involve promoting formation and hyperstabilization of microtubules, thereby preventing the disassembly of microtubules necessary for completion of cell division. It also has been reported that Taxol induces expression of cytokines, affects the activity of kinases and blocks processes essential for metastasis, in as yet uncharacterized mechanisms of action.

Taxol has attracted unusually strong scientific attention, not only because of its unique antiproliferative mechanism of action, but also because it is active against nearly all cancers against which it has been tested and because it has been discovered to be an analog of numerous closely related compounds occurring naturally. These compounds, taxanes, are now recognized as a new class of anticancer compounds.

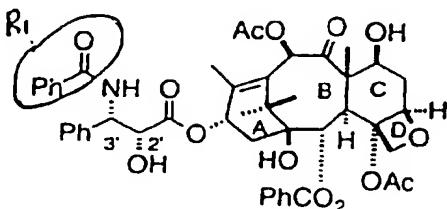
Taxol's strength against cancers of diverse tissue origin also represents a significant drawback. An ideal anticancer agent has tissue specificity, thereby reducing side-effects on normal (dividing) cells. Taxol analogs with tissue specificity therefore are desired. Another drawback of Taxol is its extreme insolubility. Taxol can be administered effectively in a solvent including cremophor, which combination can provoke severe hypersensitive immune responses. As a result of these drawbacks, and also as a result of the potential for modifying Taxol at numerous sites as demonstrated by other naturally-occurring taxanes with anticancer activity, a search for more selective taxanes was launched.

To date, more than 200 taxanes have been synthesized (or isolated) and tested *in vitro* or *in vivo* for anticancer activity. The results, however, have been so disappointing that the National Cancer Institute (NCI) generally no longer is interested in testing Taxol analogs. In general with Taxol analogs, the solubility problems remain, and/or potency is sharply reduced, and/or selectivity

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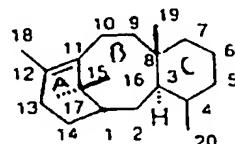
is not improved, and/or the ratio of the median toxic dose to the median effective dose ("therapeutic index") is unacceptably reduced.

Taxol has the following formula:



Taxanes have the basic three ring structure (A, B and C), substituted or unsubstituted.

10 Taxol's carbons are numbered conventionally as follows:



15 Based upon the taxanes tested to date, as many questions have been raised as have been answered, and general rules have not been fashioned easily in predicting selectivity, activity and solubility. Firstly, no rules have emerged regarding selectivity. Those taxanes that are strongly active appear to have activity as broad as Taxol's activity, and no headway appears to have been made in terms of developing a more selective Taxol analog.

20 Some information about activity has emerged. Numerous substitutions have been made at C7, C9, C10, C19, R, and combinations thereof while retaining significant, but usually reduced, activity. Substitutions at C2, C4 and 2'OH, however, are generally not tolerated. These conclusions are only generalities, for example, because some substitutions at C9-C10 (cyclic derivatives) are not tolerated and some substitutions at C2 (meta substitutions on the phenyl) are tolerated. Likewise, 25 the C13 side chain and, in particular, the 2'OH are required, although the minimum structural requirements of the side chain have not been determined for therapeutic efficacy.

Attempts to improve Taxol's solubility have not resulted in successful clinical products. One approach has been to manufacture prodrugs of Taxol, which prodrugs undergo *in vivo* transformation into Taxol and some other product. Attempts were made to esterify the C7 hydroxy and 2' hydroxy groups, with the hope that the bond would be stable in solution (to permit preferred administration modes -i.v. over at least 24 hours) but would cleave readily *in vivo*. The groups tested were all hydrophilic and included amines, short carboxylic acids (using e.g. succinic anhydride and glutaric

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anhydride), sulfonic acids, amino acids and phosphates. Generally, activity was reduced although some success was obtained with certain derivatives. Again, no particular pattern emerged permitting one to predict reliably which groups could be substituted on Taxol to yield a therapeutically useful product, although it was suggested that the 2' OH derivatives may cleave more easily than the C7 OH derivatives.

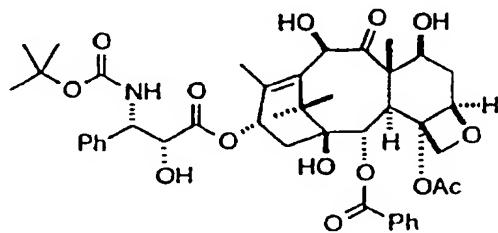
Several other factors add to the problem of predicting which Taxol analogs will be effective. Multiple mechanisms of action have been proposed in the literature, and a change in one position may have no effect on activity on one such mechanism but may eliminate activity on another mechanism. In addition, changes that favorably influence activity may unfavorably influence bioavailability. For example, Taxol affects microtubule formation inside a cell, but a change in structure that increases intracellular activity may adversely affect the ability of Taxol to gain entry into a cell. Taxol also is known to bind to proteins, and the effect on activity that results from a change in Taxol's binding to protein (in terms of conformation, cellular absorption and solubility) is unknown.

It has been reported that Taxol does not get into the brain, apparently excluded by the blood brain barrier. It is not known why this is so, as Taxol is lipophilic, gets into cells and might be expected to cross the blood brain barrier.

Among the most promising of the two hundred analogs tested is Taxotere (docetaxel), because of its slightly increased activity and solubility. Oddly, however, Taxotere differs from Taxol at sites which typically do not have a strong influence on activity, and one would not predict the improvements in Taxotere from these differences, even in hindsight.

Taxotere has the following formula:

25



DHA (docosahexaenoic acid) is a 22 carbon naturally-occurring, unbranched fatty acid that previously has been attached to drugs to help deliver them across the blood brain barrier. DHA is attached via the acid group to hydrophilic drugs and renders these drugs more hydrophobic (lipophilic). DHA is an important constituent of the brain and recently has been approved in Europe

as an additive to infant formula. It is present in the milk of lactating women. The mechanism of action by which DHA helps drugs conjugated to it cross the blood brain barrier is unknown.

### Summary of the Invention

The present invention involves the unexpected finding that conjugates of pharmaceutical agents and a highly lipophilic group, a C22 unbranched carbon chain, have a different *selectivity* relative to the unconjugated pharmaceutical agents. The conjugates, in general, render the activity of these compounds selective for colon tissue, breast tissue and central nervous system tissue ("targeted tissues"). The conjugates, also unexpectedly, restrict the activity of these compounds to cell types within these tissue categories relative to that of the unconjugated pharmaceutical agents. The conjugates, further unexpectedly, reduce sharply the activity of these compounds relative to that of the unconjugated pharmaceutical agents in most cell lines of tissue types *other than* colon, breast, and central nervous system, thereby reducing potential side effects of the conjugates versus those of the unconjugated pharmaceutical agents. The therapeutic index of the conjugates may be improved, versus that of the unconjugated pharmaceutical agents.

According to one aspect of the invention, a method is provided for targeting a pharmaceutical agent to a noncentral nervous system tissue to treat a noncentral nervous system condition. A covalent conjugate of *cis*-docosahexaenoic acid and a pharmaceutical agent effective for treating said condition is administered to a subject in need of such treatment. Preferably, the conjugate consists only of *cis*-docosahexaenoic acid and the pharmaceutical agent, wherein the *cis*-docosahexaenoic acid is conjugated directly to the pharmaceutical agent, free of linker, for example via the carboxylic acid group of the *cis*-docosahexaenoic acid and a reactive group such as a free amino or hydroxyl group of the pharmaceutical agent. In preferred embodiments, the tissue is breast tissue, gastrointestinal tissue and ovarian tissue and the condition calls for treatment of breast tissue, gastrointestinal tissue or ovarian tissue, respectively.

The conjugates of the invention can be isolated conjugates. An isolated conjugate is one which is separated from other different docosahexaenoic acid-pharmaceutical agent conjugates.

The pharmaceutical agent may be any pharmacological compound or diagnostic agent, as desired. The pharmaceutical agent, of course, has an activity outside of the central nervous system.

Examples of catagories of pharmaceutical agents include: adrenergic agent; adrenocortical steroid; adrenocortical suppressant; alcohol deterrent; aldosterone antagonist; amino acid; ammonia detoxicant; anabolic; analeptic; analgesic; androgen; anesthesia, adjunct to; anesthetic;

anorectic; antagonist; anterior pituitary suppressant; anthelmintic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-androgen; anti-anemic; anti-anginal; anti-anxiety; anti-arthritis; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholelithic; anticholelithogenic; anticholinergic; anticoagulant; anticoccidal; anticonvulsant; antidepressant; 5 antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, topical; anti-inflammatory; antikeratinizing agent; antimarial; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobessional 10 agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy; antiprotozoal; antipruritic; antipsychotic; antirheumatic; antischistosomal; antisborrheic; antisecretory; antispasmodic; antithrombotic; antitussive; anti-ulcerative; anti-urolithic; antiviral; appetite suppressant; benign prostatic hyperplasia therapy agent; blood glucose regulator; bone resorption inhibitor; bronchodilator; carbonic anhydrase inhibitor; cardiac 15 depressant; cardioprotectant; cardiotonic; cardiovascular agent; choleric; cholinergic; cholinergic agonist; cholinesterase deactivator; coccidiostat; cognition adjuvant; cognition enhancer; depressant; diagnostic aid; diuretic; dopaminergic agent; ectoparasiticide; emetic; enzyme inhibitor; estrogen; fibrinolytic; fluorescent agent; free oxygen radical scavenger; gastrointestinal motility effector; glucocorticoid; gonad-stimulating principle; hair growth stimulant; hemostatic; histamine H<sub>2</sub> 20 receptor antagonists; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; impotence therapy adjunct; inhibitor; keratolytic; LNRH agonist; liver disorder treatment; luteolysin; memory adjuvant; mental performance enhancer; mood regulator; mucolytic; mucosal protective agent; mydriatic; nasal decongestant; neuromuscular blocking agent; 25 neuroprotective; NMDA antagonist; non-hormonal sterol derivative; oxytocic; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; post-stroke and post-head trauma treatment; potentiator; progestin; prostaglandin; prostate growth inhibitor; prothyrotropin; psychotropic; pulmonary surface; radioactive agent; regulator; relaxant; repartitioning agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine 30 A<sub>1</sub> antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; steroid; stimulant; suppressant; symptomatic multiple sclerosis; synergist; thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; treatment of amyotrophic lateral sclerosis; treatment of cerebral

ischemia; treatment of Paget's disease; treatment of unstable angina; uricosuric; vasoconstrictor; vasodilator; vulnerary; wound healing agent; xanthine oxidase inhibitor.

In important embodiments of the invention, the pharmaceutical agent is a non anti-cancer agent. In another embodiment of the invention, the pharmaceutical agent is an anti-cancer agent.

5 Examples of anti-cancer agents are described in greater detail in the specification. Included specifically are the taxanes (e.g., Taxol and Taxotere). Conjugates of *cis*-docosahexaenoic acid and taxoids also are embraced by the invention.

*Cis*-docosahexaenoic acid previously has been conjugated to drugs that are active in the central nervous system. The present invention contemplates the use of *cis*-docosahexaenoic acid in 10 the manufacture of a medicament for treating a noncentral nervous system condition. The invention further contemplates compositions of matter that are covalent conjugates of *cis*-docosahexaenoic acid and noncentral nervous system active pharmaceutical agents. A noncentral nervous system active pharmaceutical agent is one that has no function or use in the central nervous system. Its only therapeutic use is outside of the central nervous system. Examples of such agents include, but are 15 not limited to: Blood glucose regulators, such as tolazamide, tolbutamide, chlorpropamide, acetohexamide, and, glipizide; HMGCoA reductase inhibitors, such as Lovastatin (Mevacor), Simvastatin (Zocor), Pravastatin (Pravachol), and, Fluvastatin (Lescol); Muscosal Protectives, such as Misoprostol (Cytotec); Gastrointestinal motility affectors, such as Cisapride (Propulsid), Metoclopramide (Reglan), and, Hyoscymine (Levsin); Antidiarrheals, such as Diphenoxylate 20 hydrochloride (Lomotil), Metronidazole (Flagyl), Methylprednisolone (Medrol), and, Sulfasalazine (Azulfidine); and Hormones for treating, inter alia, ovarian conditions, such as Progesterone, Norgestrel, Norethynodrel, Norethindrone, Levonorgestrel, Ethynodiol, Mestranol, Estrone, Equilin, 17 alpha dihydroequilin, equilenin, 17 alpha dihydroequilenin, 17 alpha estradiol, 27 beta estradiol, Leuprolide (Lupron), Testolactone, Climiphene, urofollitropin, bromocriptine, gonadorelin, danazol, 25 dehydroepiandrosterone, androstenedione, dihydrotestosterone, Relaxin, folliculostatin, Follicle regulatory protein, Gonadocrinins, Oocyte maturation inhibitor, and, Insulin growth factor. Other compounds are detailed below.

The methods and/or products of the invention are useful for treating a variety of medical conditions including conditions involving abnormal mammalian-cell proliferation. They further are 30 useful in treating diabetes and its complications, excess acid secretion, cardiovascular conditions involving cholesterol (e.g., hyperlipidemia and hypercholesterolemia), diarrhea, ovarian diseases (e.g. endometriosis, ovarian cysts, etc.) and as contraceptive agents. Other conditions treatable

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according to the invention will be apparent to those skilled in the art based upon the disclosure and lists of compounds provided.

The methods and/or products of the invention also are useful in treating conditions specific to noncentral nervous system tissue. Such conditions can be specific to breast tissue, gastrointestinal tissue and ovarian tissue. The tissue also may be other noncentral nervous system tissues. Noncentral nervous system tissue includes tissue of the: Blood and Blood Forming system: including platelets, blood vessel wall, and bone marrow; Cardiovascular system: including heart and vascular system; Digestive and excretory system: including alimentary tract, biliary tract, kidney, liver, pancreas and urinary tract; Endocrine system: including adrenal gland, kidney, ovary, pituitary gland, renal gland, salivary gland, sebaceous gland, testis, thymus gland and thyroid gland; Musclar system: including muscles that move the body. Reproductive System: including breast, ovary, penis and uterus; Respiratory system: including bronchus, lung and trachea; Skeletal system: including bones and joints; Tissue, fiber, and integumentary system: including adipose tissue, cartilage, connective tissue, cuticle, dermis, epidermis, epithelium, fascia, hair follicle, ligament, bone marrow, melanin, melanocyte, mucous membrane, skin, soft tissue, synovial capsule and tendon.

#### Brief Description of the Drawings

Figure 1 is a graph plotting concentration of conjugate 1 versus percent growth of leukemia cells.

Figure 2 is a graph plotting concentration of conjugate 1 versus percent growth of non-small cell lung cancer cells.

Figure 3 is a graph plotting concentration of conjugate 1 versus percent growth of colon cancer cells.

Figure 4 is a graph plotting concentration of conjugate 1 versus percent growth of CNS cancer cells.

Figure 5 is a graph plotting concentration of conjugate 1 versus percent growth of melanoma cells.

Figure 6 is a graph plotting concentration of conjugate 1 versus percent growth of ovarian cancer cells.

Figure 7 is a graph plotting concentration of conjugate 1 versus percent growth of renal cancer cells.

Figure 8 is a graph plotting concentration of conjugate 1 versus percent growth of prostate

cancer cells.

Figure 9 is a graph plotting concentration of conjugate 1 versus percent growth of breast cancer cells.

5 Figure 10 is a graph plotting concentration of conjugate 2 versus percent growth of leukemia cells.

Figure 11 is a graph plotting concentration of conjugate 2 versus percent growth of non-small cell lung cancer cells.

Figure 12 is a graph plotting concentration of conjugate 2 versus percent growth of colon cancer cells.

10 Figure 13 is a graph plotting concentration of conjugate 2 versus percent growth of CNS cancer cells.

Figure 14 is a graph plotting concentration of conjugate 2 versus percent growth of melanoma cells.

15 Figure 15 is a graph plotting concentration of conjugate 2 versus percent growth of ovarian cancer cells.

Figure 16 is a graph plotting concentration of conjugate 2 versus percent growth of renal cancer cells.

Figure 17 is a graph plotting concentration of conjugate 2 versus percent growth of prostate cancer cells.

20 Figure 18 is a graph plotting concentration of conjugate 2 versus percent growth of breast cancer cells.

Figure 19 is a graph plotting concentration of Taxol versus percent growth of leukemia cells.

Figure 20 is a graph plotting concentration of Taxol versus percent growth of non-small cell lung cancer cells.

25 Figure 21 is a graph plotting concentration of Taxol versus percent growth of colon cancer cells.

Figure 22 is a graph plotting concentration of Taxol versus percent growth of CNS cancer cells.

30 Figure 23 is a graph plotting concentration of Taxol versus percent growth of melanoma cells.

Figure 24 is a graph plotting concentration of Taxol versus percent growth of ovarian cancer cells.

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Figure 25 is a graph plotting concentration of Taxol versus percent growth of renal cancer cells.

Figure 26 is a graph plotting concentration of Taxol versus percent growth of prostate cancer cells.

5       Figure 27 is a graph plotting concentration of Taxol versus percent growth of breast cancer cells.

#### Detailed Description of the Invention

Cis-docosahexaenoic acid (DHA) is a naturally occurring fatty acid. It is an unbranched 10 chain fatty acid with six double bonds, all *cis*. Its structure is as follows:



DHA can be isolated, for example, from fish oil or can be chemically synthesized. These 15 methods, however, can generate *trans* isomers, which are difficult and expensive to separate and which may present safety problems in humans. The preferred method of production is biological synthesis to produce the all *cis* isomer. The preferred source of DHA is from Martek Biosciences Corporation of Columbia, Maryland. Martek has a patented system for manufacturing DHA using microalgae which synthesize only a single isomer of DHA, the all *cis* isomer. Martek's patents 20 include U.S. Pat. Nos. 5,374,657, 5,492,938, 5,407,957 and 5,397,591.

DHA also is present in the milk of lactating women, and Martek's licensee has obtained approval in Europe of DHA as a nutritional supplement for infant formula.

It is known that DHA can be unstable in the presence of oxygen. To stabilize DHA and its conjugates it is important to add anti-oxidants to the material after it is synthesized. One method of 25 stabilization is to make-up the newly synthesized material in the following solution:

100 g neat DHA-taxol plus 100 g of vehicle (100ml propylene glycol, 70 mg alph-tocopherol, 5 mg dialaurylthiodipropionic acid, 50 mg ascorbic acid) prepared and held under argon in amber, sealed vials and stored at four degrees centigrade. The following anti-oxidants may also be employed: ascorbic acid, ascorbyl palmitate, dilauryl ascorbate, hydroquinone, butylated hydroxyanisole, 30 sodium meta bisulfite,  $\beta$ -carotene and  $\alpha$ -tocopherol. A heavy metal chelator such as ethylenediamine tetra-acetic acid (EDTA) may also be used.

Paclitaxel was first isolated from the bark of Taxus brevifolia (Wani et al., J. Am. Chem.

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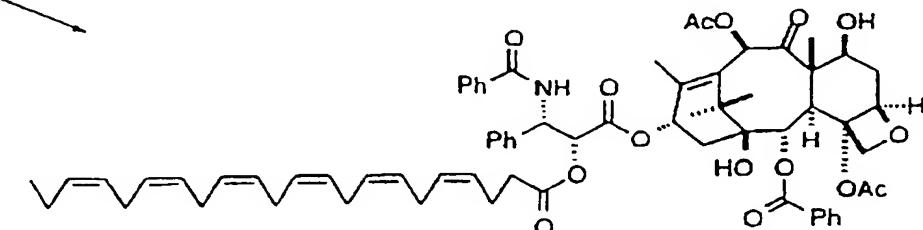
Soc., 93, 2325, 1971). Its isolation and synthesis have been reported extensively in the literature. Applicants obtained paclitaxel from a commercial source, Hauser Laboratories, of Boulder, Colorado.

Example 1

5

TAXOL

10



**conjugate 1**

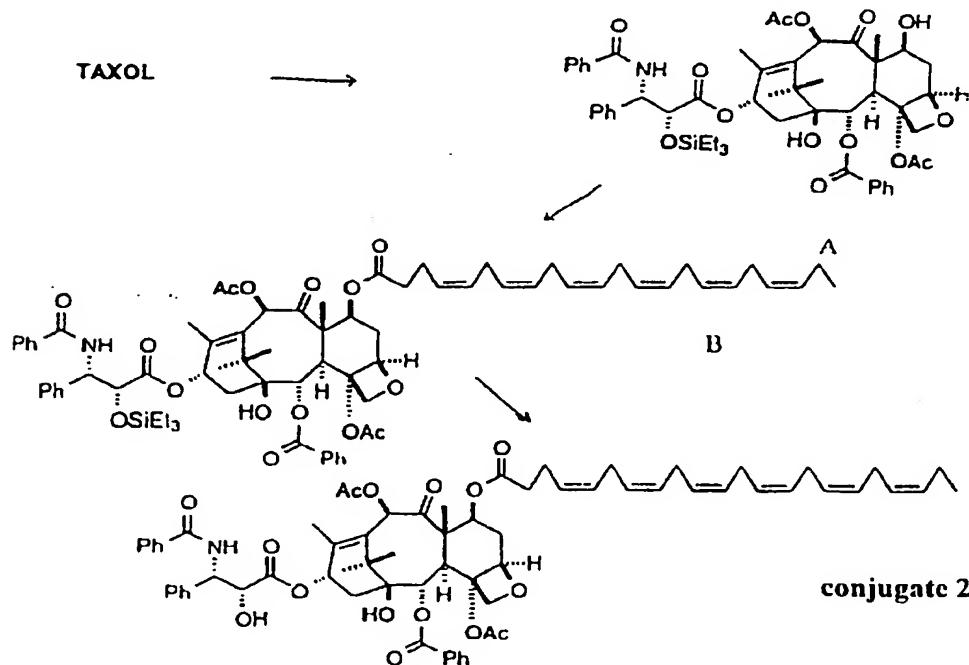
A solution of Taxol (41 $\mu$ mol) in methylene chloride (2.5mL) under argon was mixed with 4-dimethylaminopyridine (41 $\mu$ mol), dicyclohexylcarbodiimide (82 $\mu$ mol), and DHA (41 $\mu$ mol) and 15 the reaction mixture was stirred at ambient temperature for two hours. Following dilution with ether, the reaction mixture was washed with 5% hydrochloric acid, water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue produced 45mg (94%) of crystalline Taxol-DHA conjugate 1.

Example 2

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25

30



**conjugate 2**

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The production of analog 2 involves several steps including a number of protection-acylation-deprotection steps. A solution of Taxol (59 $\mu$ mol) in methylene chloride (2.5mL) was mixed at ambient temperature under argon with imidazole (147 $\mu$ mol) and triethylsilyl chloride (147 $\mu$ mol). The reaction mixture was stirred for thirty minutes, diluted with additional 5 methylene chloride, washed with water, saturated aqueous sodium chloride, dried, and concentrated. Chromatography of the residue produced 50mg (88%) of intermediate A plus 5mg of the 2', 7-di(triethylsilyl) ether derivative. A solution of intermediate A (52 $\mu$ mol) in methylene chloride (3mL) was mixed at ambient temperature under argon with 4-dimethylaminopyridine (52 $\mu$ mol), dicyclohexylcarbodiimide (104 $\mu$ mol), and DHA (52 $\mu$ mol). The reaction mixture was stirred for ten 10 hours, diluted with ether, passed through celite, and concentrated. Chromatography of the residue produced 65.9mg of intermediate B. A solution of intermediate B (51 $\mu$ mol) in acetonitrile (2mL) at 0°C under argon was mixed with 49% aqueous HF (0.2mL) and the reaction mixture was stirred for one hour. After dilution with ether, the reaction mixture was washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue produced 15 44.6mg (75%) of Taxol-DHA conjugate 2.

### Example 3

Conjugates 1 and 2 were sent to the United States National Cancer Institute (NCI) for screening in the NCI's anticancer screening program. The conjugates were provided in ethanol 20 (approximately 40mg analog/2ml ethanol). The conjugates were sealed in vials under argon to avoid exposure of the conjugates to oxygen because the conjugates were believed to be sensitive to oxygen. Instructions were provided to store at 4°C and to open the vials only when ready for immediate experimental use. Instructions also were provided to use the ethanol solutions containing the conjugates directly or to dissolve the analogs further in DMSO (dimethylsulfoxide) at 25 appropriate concentrations, with vortexing if necessary for adequate dispersal.

The activities of conjugates 1 and 2 were tested against 57 cancer cell lines. The results are presented in Figs. 1-9 for conjugate 1, Figs. 10-18 for conjugate 2 and Figs 19-27 for Taxol. To understand the data, reference is made to the guides provided by the NCI, excerpted as follows:

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The Calculated Measurement of Effect: Percentage Growth (PG)

The measured effect of the compound on a cell line is currently calculated according to one or the other of the following two expressions:

5 If (Mean OD<sub>test</sub> - Mean OD<sub>tzero</sub>) ≥ 0, then

$$PG = 100 \times (\text{Mean OD}_{\text{test}} - \text{Mean OD}_{\text{tzero}}) / (\text{Mean OD}_{\text{ctrl}} - \text{Mean OD}_{\text{tzero}})$$

If (Mean OD<sub>test</sub> - Mean OD<sub>tzero</sub>) < 0, then

10  $PG = 100 \times (\text{Mean OD}_{\text{test}} - \text{Mean OD}_{\text{tzero}}) / \text{Mean OD}_{\text{tzero}}$

Where:

15 Mean OD<sub>tzero</sub> = The average of optical density measurements of SRB-derived color just before exposure of cells to the test compound.

Mean OD<sub>test</sub> = The average of optical density measurements of SRB-derived color after 48 hours exposure of cells to the test compound.

20 Mean OD<sub>ctrl</sub> = The average of optical density measurements of SRB-derived color after 48 hours with no exposure of cells to the test compound.

25 Experimental data was collected against each cell line. ... Each concentration is expressed as the log<sub>10</sub> (molar or µg/ml). ... The response parameters GI50, TGI, and LC50 are interpolated values representing the concentrations at which the PG is +50, 0, and -50, respectively. Sometimes these response parameters cannot be obtained by interpolation. If, for instance, all of the PGs in a given row exceed +50, then none of the three parameters can be obtained by interpolation. In such a case, the value given for each response parameter is the highest concentration tested. ... This practice is extended similarly to the other possible situations where a response parameter cannot be obtained 30 by interpolation.

Dose-Response Curves:

The dose-response curve page of the data package is created by plotting the PGs against the  $\log_{10}$  of the corresponding concentration for every cell line. The cell line curves are grouped by subpanel. Horizontal lines are provided at the PG values of +50, 0, and -50. The concentrations corresponding to points where the curves cross these lines are the GI50, TGI and LC50, respectively.

Several important distinctions are apparent from the data. Most important, the patterns of anticancer activity for conjugates 1 and 2 differ from that of Taxol. In one sense, conjugates 1 and 2 are effective anticancer agents against a more restricted set of cancer cell lines. For example, conjugates 1 and 2 were not very effective against any of the six leukemia cancer cell lines tested, whereas Taxol was somewhat effective against all four leukemia cell lines against which Taxol was tested. (See Figs. 1, 10 and 19.)

The relative activity against members within a class of cancers also was altered. For example, at TGI (horizontal line at zero in the graphs), Taxol was more effective against non-small cell lung cancer line H522 than against H460 (by about 3 logs), whereas conjugates 1 and 2 were slightly more effective against H460 than H522. As another example, Taxol was least effective at TGI against CNSU251, whereas conjugate 1 was most effective against CNSU251 and conjugate 2 was also very effective against CNSU251 (relative to other CNS cell lines). As a further example, Taxol was equivalent in activity toward MDA-N and MDA-MB-435 breast cancer cell lines at all concentrations tested, whereas conjugates 1 and 2 were more effective against MDA-N than MDA-MB-435 at all concentrations tested.

To further illustrate the differences in the activity of conjugates 1 and 2 versus that of Taxol, the NCI subjected the data to a statistical analysis designed by the NCI to reflect differences in the pattern of activity of anticancer agents. Conjugate 1 and conjugate 2 were determined to be statistically different in their pattern of activity versus Taxol in this unique measurement by the NCI.

It also is to be noted that, in general, conjugates 1 and 2 were one thousand to ten thousand times less potent than Taxol for many cell lines tested. This reduction in activity is important, especially since conjugates 1 and 2 maintained strong activity against some cell lines. Conjugates 1 and 2 will be sufficiently active against certain cell lines, but will have, on average, a substantially and disproportionately lower activity against other cell lines, reducing potential side effects. For

example, the TGI for Taxol against CNS SF-539 is -6.95, and the TGI for conjugate 1 against this cell line is -5.13 and for conjugate 2 is -5.53. (In other words, the activity of the conjugates was reduced versus that of Taxol by less than 2 logs). The GI50 for Taxol against CNS SF 539 is -7.52, whereas the GI50s for conjugates 1 and 2 are -6.22 and -5.56, respectively (again less than 2 logs difference). In contrast, Taxol has a GI50 for cell line CNSSF 268 of less than -10.0, whereas conjugates 1 and 2 have GI50s for CNSSF 268 of 5.36 and 5.28, respectively. This represents a reduction of activity in the conjugates vs. that of Taxol by at least about 5 logs activity! On average, the GI50 for Taxol across all cell lines tested is at least -9.19. (It is probably much higher since concentrations less than -10 were not tested, and if Taxol was active at -10.0, -10 (instead of the actual lower value) was used in calculating the average of -9.19. There were 27 instances when this occurred.) The average GI50s for conjugates 1 and 2 , on the other hand, were 5.49 and 5.22, respectively. Therefore, the average difference in activity for Taxol vs. the conjugates is *at least* between 3 and 4 logs. Thus, the sharp reduction in the activity of the conjugates against many cell lines vs. a lesser reduction for other cell lines is expected to reduce the potential side effects of the conjugates versus those of Taxol at effective doses.

Cancers other than CNS, breast and colon cancer can be treated. For example, there was activity against non-small cell lung cancer cells, melanoma cells and ovarian cancer cells. However, the activity was relatively reduced and was extremely specific, limiting the utility of the conjugates for treating generally such cancers. In any event, cancer patients could be evaluated to determine if a conjugate is strongly active against the patient's cancer prior to selecting the conjugate as the anti-cancer agent of choice for that patient.

The foregoing experiments establish that DHA analogs have altered specificity versus that of Taxol for cancer cell lines. Because of this altered specificity, it also is clear that the conjugates themselves are gaining access into the target cells (as opposed to simply releasing Taxol into the environment outside of the cell). Thus, the DHA moiety appears to selectively target certain cell types as opposed to others. The ability of the conjugates to gain entry into the cells was unknown prior to the invention, and the ability of the DHA moiety to selectively target certain cell types was unexpected.

The same is true of DHA-Taxotere covalent conjugates, examples of which are presented below. Taxotere's synthesis has been reported extensively in the literature. One example is Kanazawa, A. et al., J. Organic Chem. 1994, Vol. 59, pp. 1238-1240.

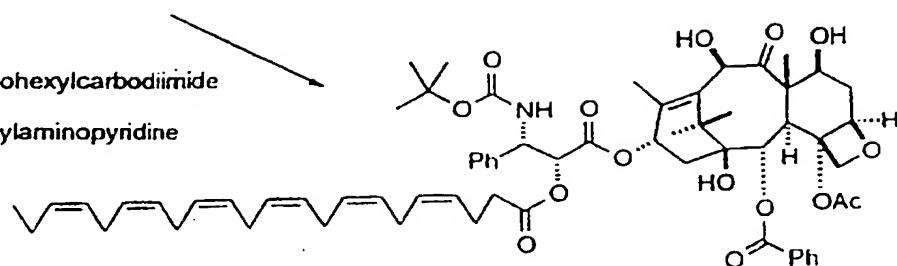
- 15 -

Example 4

## TAXOTERE

5

DHA / dicyclohexylcarbodiimide  
4-dimethylaminopyridine



10

**conjugate 3**

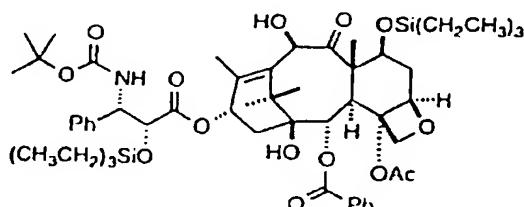
A solution of Taxotere in methylene chloride under argon is mixed with 4-dimethylaminopyridine, dicyclohexylcarbodiimide, and DHA. The reaction mixture is stirred at ambient temperature. Radial chromatography of the residue is performed to produce Taxotere-DHA conjugate 3.

Example 5

## TAXOTERE

triethylsilyl chloride  
imidazole

20



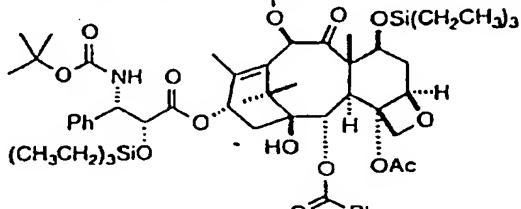
C

DHA / dicyclohexylcarbodiimide

25

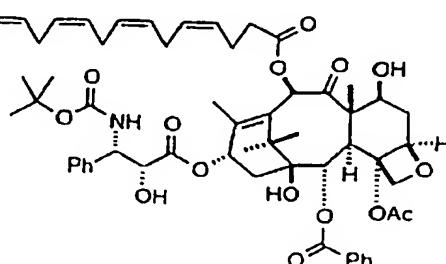
4-dimethylaminopyridine

D



aqueous HF

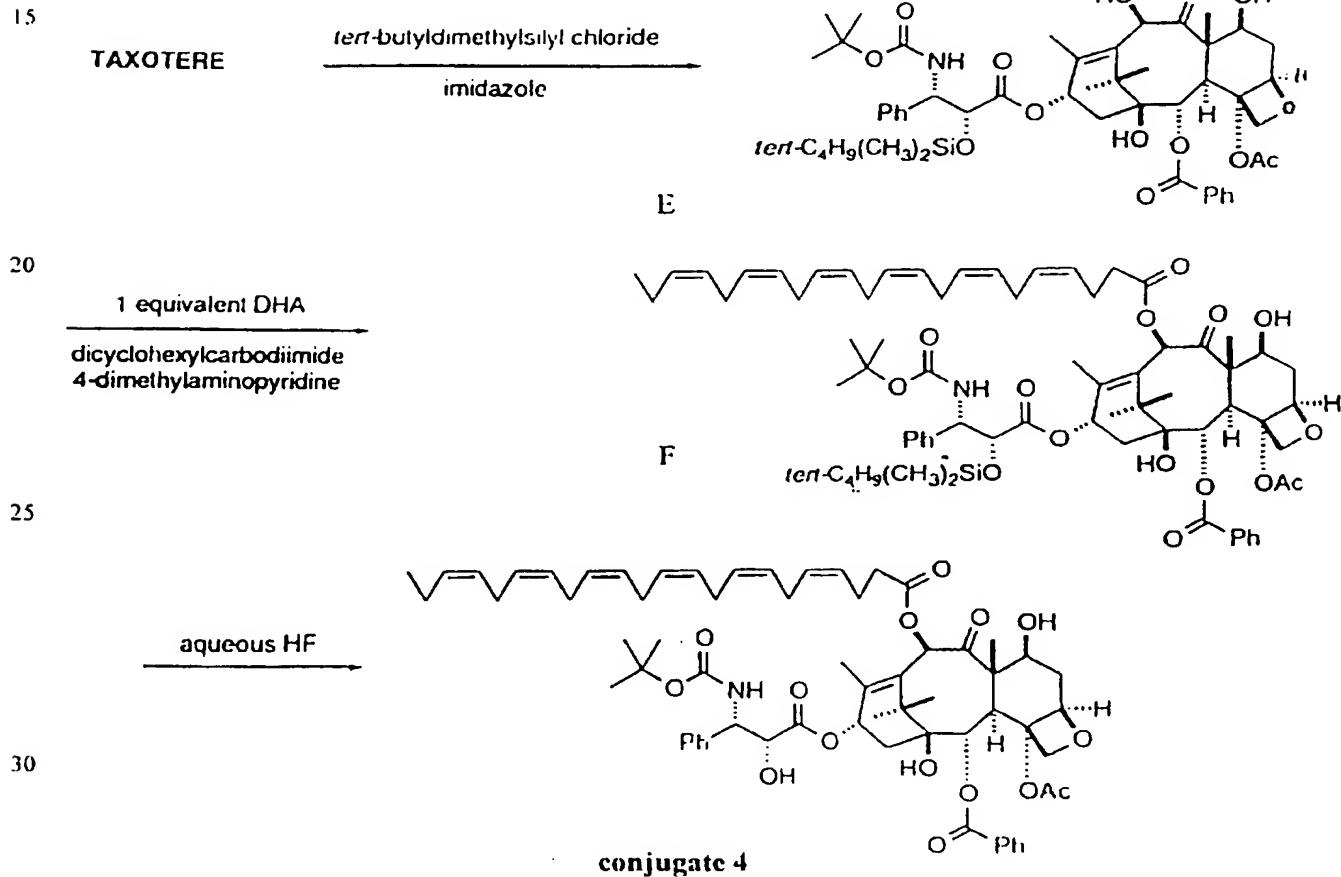
30

**conjugate 4**

- 16 -

A solution of Taxotere in dimethylformamide is mixed at ambient temperature under argon with imidazole and triethylsilyl chloride. The reaction mixture is stirred at ambient temperature, diluted with methylene chloride, washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce intermediate C. A 5 solution of intermediate C in methylene chloride is mixed at ambient temperature under argon with 4 dimethylaminopyridine, dicyclohexylcarbodiimide, and DHA. The reaction mixture is stirred at ambient temperature, diluted with ether, passed through celite, and concentrated. Radial chromatography of the residue is performed to produce intermediate D. A solution of intermediate 10 D in acetonitrile at 0°C under argon is mixed with 49% aqueous HF and the reaction mixture is stirred at the same temperature. After dilution with ether, the reaction mixture is washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce Taxotere-DHA conjugate 4.

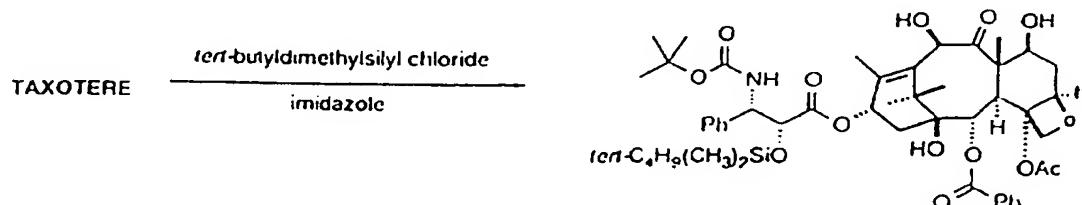
Example 6



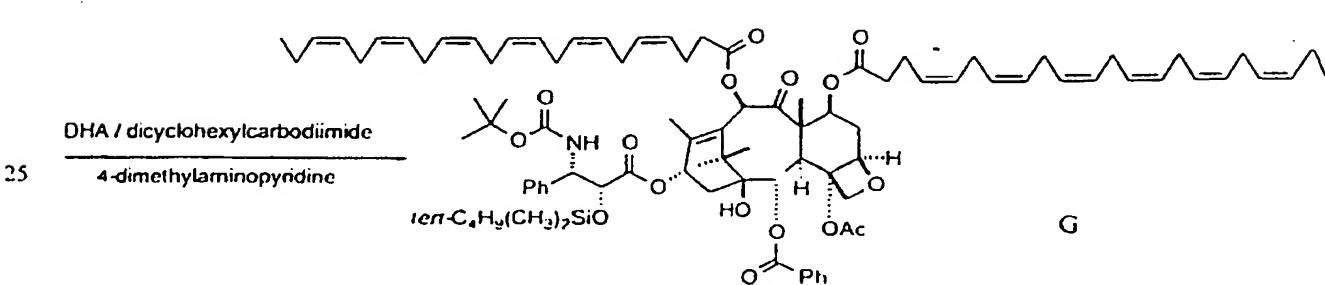
A solution of Taxotere in dimethylformamide is mixed at ambient temperature under argon with imidazole and *tert*-butyldimethylsilyl chloride. The reaction mixture is stirred at ambient temperature, diluted with methylene chloride, washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce intermediate E. A solution of intermediate E in methylene chloride is mixed at ambient temperature under argon with 4-dimethylaminopyridine, dicyclohexylcarbodiimide, and 1 equivalent of DHA. The reaction mixture is stirred at ambient temperature, diluted with ether, passed through celite, and concentrated. Radial chromatography of the residue is performed to produce intermediate F. (Intermediate H also is obtained and used in Example 8 below.) A solution of intermediate F in acetonitrile at 0°C under argon is mixed with aqueous HF and the reaction mixture is stirred at the same temperature. After dilution with ether, the reaction mixture is washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce Taxotere-DHA conjugate 4.

### Example 7

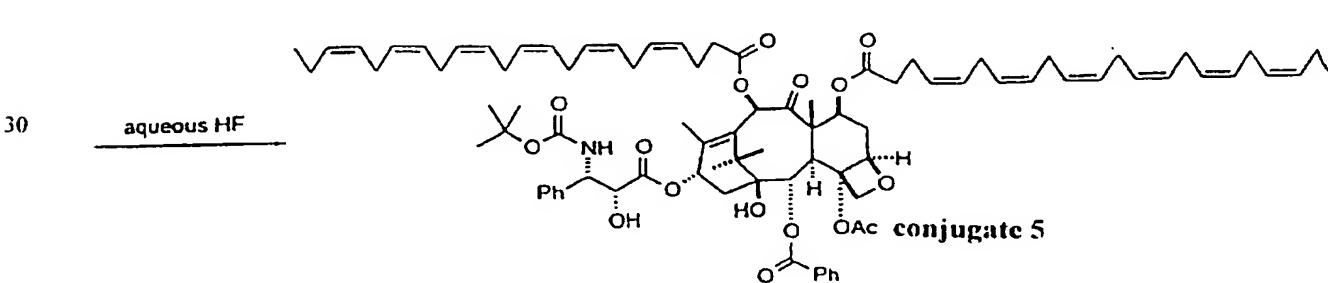
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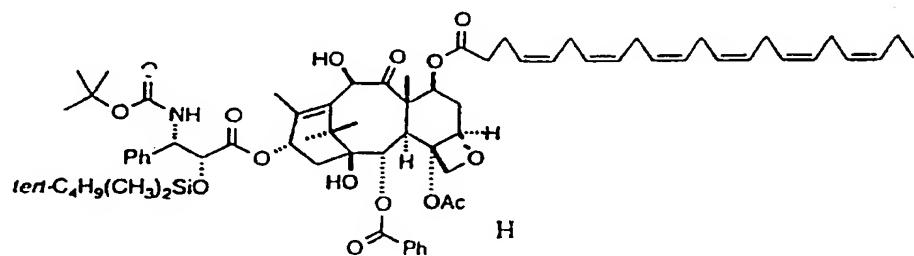
30

A solution of Taxotere in dimethylformamide is mixed at ambient temperature under argon with imidazole and *tert*-butyldimethylsilyl chloride. The reaction mixture is stirred at ambient temperature, diluted with methylene chloride, washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce intermediate E. A solution of intermediate E in methylene chloride is mixed at ambient temperature under argon with 4-dimethylaminopyridine, dicyclohexylcarbodiimide, and DHA. The reaction mixture is stirred at ambient temperature, diluted with ether, passed through celite, and concentrated. Radial chromatography of the residue is performed to produce intermediate G. A solution of intermediate G in acetonitrile at 0°C under argon is mixed with aqueous HF and the reaction mixture is stirred at the same temperature. After dilution with ether, the reaction mixture is washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce Taxotere-DHA conjugate S.

**Example 8**

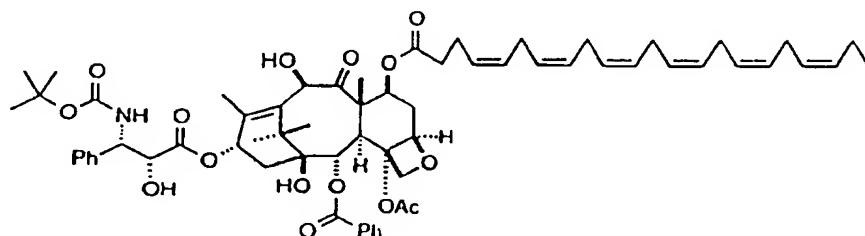
15

1 equivalent DHA  
dicyclohexylcarbodiimide  
4-dimethylaminopyridine



20

aqueous HF



25

30

**conjugate 6**

A solution of taxotere in dimethylformamide is mixed at ambient temperature under argon with imidazole and *tert*-butyldimethylsilyl chloride. The reaction mixture is stirred at ambient temperature, diluted with methylene chloride, washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce 5 intermediate E. A solution of intermediate E in methylene chloride is mixed at ambient temperature under argon with 4-dimethylaminopyridine, dicyclohexylcarbodiimide, and 1 equivalent of DHA. The reaction mixture is stirred at ambient temperature, diluted with ether, passed through celite, and concentrated. Radial chromatography of the residue is performed to produce intermediate H (and 10 intermediate F which was used above on Example 6. A solution of intermediate H in acetonitrile at 0°C under argon is mixed with aqueous HF and the reaction mixture is stirred at the same temperature. After dilution with ether, the reaction mixture is washed with water, saturated aqueous sodium chloride, dried, and concentrated. Radial chromatography of the residue is performed to produce Taxotere-DHA conjugate 6.

DHA may be conjugated to virtually any drug compound or diagnostic agent and used 15 according to the methods of the present invention so long as the pharmaceutical agent has a use outside of the central nervous system. Pharmaceutical agents include the following categories and specific examples. It is not intended that the category be limited by the specific examples. Those of ordinary skill in the art will be able to identify readily those pharmaceutical agents that have utility outside of the central nervous system. Those of ordinary skill in the art will recognize also 20 numerous other compounds that fall within the categories and that are useful according to the invention.

Adrenergic: Adrenalone; Amidephrine Mesylate; Apraclonidine Hydrochloride; Brimonidine Tartrate; Dapiprazole Hydrochloride; Deterenol Hydrochloride; Dipivefrin; Dopamine Hydrochloride; Ephedrine Sulfate; Epinephrine; Epinephrine Bitartrate; Epinephryl Borate; Esproquin Hydrochloride; Etafedrine Hydrochloride; Hydroxyamphetamine Hydrobromide; Levonordefrin; Mephentermine Sulfate; Metaraminol Bitartrate; Metizoline Hydrochloride; Naphazoline Hydrochloride; Norepinephrine Bitartrate; Oxidopamine; Oxymetazoline Hydrochloride; Phenylephrine Hydrochloride; Phenylpropanolamine Hydrochloride; 30 Phenylpropanolamine Polistirex; Prenalterol Hydrochloride; Propylhexedrine; Pseudoephedrine Hydrochloride; Tetrahydrozoline Hydrochloride; Tramazoline Hydrochloride; Xylometazoline Hydrochloride.

Adrenocortical steroid: Ciprocinonide; Desoxycorticosterone Acetate; Desoxycorticosterone Pivalate; Dexamethasone Acetate; Fludrocortisone Acetate; Flumoxonide; Hydrocortisone Hemisuccinate; Methylprednisolone Hemisuccinate; Naflocort; Procinonide; Timobesone Acetate; Tipredane.

5

Adrenocortical suppressant: Aminoglutethimide; Trilostane.

Alcohol deterrent: Disulfiram.

10 Aldosterone antagonist: Canrenoate Potassium; Canrenone; Dicrenone; Mexrenoate Potassium; Prrenoate Potassium; Spironolactone.

Amino acid: Alanine; Aspartic Acid; Cysteine Hydrochloride; Cystine; Histidine; Isoleucine; Leucine; Lysine; Lysine Acetate; Lysine Hydrochloride; Methionine; Phenylalanine; Proline; Serine; 15 Threonine; Tryptophan; Tyrosine; Valine.

Ammonia detoxicant: Arginine: Arginine Glutamate; Arginine Hydrochloride.

Anabolic: Bolandiol Dipropionate; Bolasterone; Boldenone Undecylenate; Bolenol; Bolmantalate; 20 Ethylestrenol; Methenolone Acetate; Methenolone Enanthate; Mibolerone; Nandrolone Cyclotate; Norboletone; Pizotyline; Quinbolone; Stenbolone Acetate; Tibolone; Zeranol.

Analeptic: Modafinil.

25 Analgesic: Acetaminophen; Alfentanil Hydrochloride; Aminobenzoate Potassium; Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzodamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; Bromfenac Sodium; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; 30 Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Cipresadol Succinate; Ciramadol; Ciranadol Hydrochloride; Clonixeril; Clonixin; Codeine ; Codeine Phosphate; Codeine Sulfate; Conorphone Hydrochloride; Cyclazocine; Dexoxadrol Hydrochloride; Dexpemedolac;

Desocine; Diflunisal; Dihydrocodeine Bitartrate; Dimefadane; Dipyrone; Doxicomine Hydrochloride; Drnidene; Enadoline Hydrochloride; Epirizole; Ergotamine Tartrate; Ethoxazene Hydrochloride; Etofenamate; Eugenol; Fenoprofen; Fenoprofen Calcium; Fentanyl Citrate; Floctafenine; Flufenisal; Flunixin; Flunixin Meglumine; Flupirtine Maleate; Fluproquazone;

5 Fluradoline Hydrochloride; Flurbiprofen ; Hydromorphone Hydrochloride; Ibufenac; Indoprofen; Ketazocine; Ketorfanol; Ketorolac Tromethamine; Letimide Hydrochloride; Levomethadyl Acetate; Levomethadyl Acetate Hydrochloride; Levonantradol Hydrochloride; Levorphanol Tartrate; Lofenizole Hydrochloride; Lofentanil Oxalate; Lorcinadol; Lornoxicam; Magnesium Salicylate; Mefenamic Acid; Menabitan Hydrochloride; Meperidine Hydrochloride; Meptazinol Hydrochloride;

10 Methadone Hydrochloride; Methadyl Acetate; Methopholine; Methotrimeprazine; Metkephamid Acetate; Mimbane Hydrochloride; Mirfentanil Hydrochloride; Molinazone; Morphine Sulfate; Moxazocine; Nabitan Hydrochloride; Nalbuphine Hydrochloride; Nalmexone Hydrochloride ; Namoxyrate; Nantradol Hydrochloride; Naproxen ; Naproxen Sodium : Naproxol; Nesopam Hydrochloride; Nexteridine Hydrochloride; Noracymethadol Hydrochloride; Ocfentanil

15 Hydrochloride; Octazamide; Olvanil; Oxetorone Fumarate; Oxycodone; Oxycodone Hydrochloride; Oxycodone Terephthalate; Oxymorphone Hydrochloride; Pemedolac; Pentamorphone; Pentazocine; Pentazocine Hydrochloride; Pentazocine Lactate; Phenazopyridine Hydrochloride; Phenyramidol Hydrochloride; Picenadol Hydrochloride; Pinadoline; Pirfenidone; Piroxicam Olamine; Pravadoline Malcate; Prodilidine Hydrochloride; Profadol Hydrochloride; Propiram Fumarate; Propoxyphene

20 Hydrochloride; Propoxyphene Napsylate; Proxazole ; Proxazole Citrate ; Proxorphan Tartrate; Pyrroliphene Hydrochloride; Remifentanil Hydrochloride; Salcolex ; Salethamide Maleate; Salicylamide; Salicylate Meglumine; Salsalate ; Sodium Salicylate; Spiradoline Mesylate; Sufentanil; Sufentanil Citrate; Talmetacin ; Talniflumate ; Talosalate ; Tazadolene Succinate; Tebufelone ; Tetrydamine ; Tisurac Sodium; Tilidine Hydrochloride; Tiopinac; Tonazocine

25 Mesylate; Tramadol Hydrochloride; Trefentanil Hydrochloride; Trolaminec; Veradoline Hydrochloride; Verilopam Hydrochloride; Volazocine; Xorphanol Mesylate; Xylazine Hydrochloride; Zenazocine Mesylate; Zomepirac Sodium : Zucapsaicin.

Androgen: Fluoxymesterone; Mesterolone; Methyltestosterone; Nandrolone Decanoate; Nandrolone  
30 Phenpropionate; Nisterime Acetate; Oxandrolone; Oxymetholone; Silandrone; Stanozolol; Testosterone; Testosterone Cypionate; Testosterone Enanthate; Testosterone Ketolaurate; Testosterone Phenylacetate; Testosterone Propionate; Trestolone Acetate.

Anesthesia, adjunct to: Sodium Oxybate.

Anesthetic: Aliflurane; Benoxinate Hydrochloride; Benzocaine; Biphenamine Hydrochloride ;  
Bupivacaine Hydrochloride; Butamben; Butamben Picrate; Chloroprocaine Hydrochloride; Cocaine;  
5 Cocaine Hydrochloride; Cyclopropane; Desflurane; Dexivacaine; Diamocaine Cyclamate;  
Dibucaine; Dibucaine Hydrochloride; Dyclonine Hydrochloride; Enflurane; Ether; Ethyl Chloride;  
Etidocaine; Etoxadrol Hydrochloride; Euprocin Hydrochloride; Fluroxene; Halothane; Isobutamben;  
Isoflurane; Ketamine Hydrochloride; Levoadrol Hydrochloride ; Lidocaine; Lidocaine  
10 Hydrochloride; Mepivacaine Hydrochloride; Methohexitol Sodium; Methoxyflurane; Midazolam  
Hydrochloride; Midazolam Maleate; Minaxolone; Nitrous Oxide; Norflurane; Octodrine;  
Oxethazaine; Phencyclidine Hydrochloride; Pramoxine Hydrochloride; Prilocaine Hydrochloride;  
Procaine Hydrochloride; Propanidid; Proparacaine Hydrochloride; Propofol; Propoxycaine  
15 Hydrochloride; Pyrrocaine; Risocaine; Rodocaine; Roflurane; Salicyl Alcohol; Sevoflurane;  
Teflurane; Tetracaine; Tetracaine Hydrochloride; Thiethylal; Thiethylal Sodium; Thiopental Sodium  
; Tiletamine Hydrochloride; Zolamine Hydrochloride.

Anorectic compounds including dexfenfluramine.

Anorexic: Aminorex; Amphecloral; Chlorphentermine Hydrochloride; Clominorex; Clortermine  
20 Hydrochloride; Diethylpropion Hydrochloride; Fenfluramine Hydrochloride; Fenisorex; Fludorex;  
Fluminorex; Levamfetamine Succinate; Mazindol; Mesenorex Hydrochloride; Phenmetrazine  
Hydrochloride; Phentermine; Sibutramine Hydrochloride.

Antagonist: Atipamezole; Atosiban; Bosentan; Cimetidine; Cimetidine Hydrochloride; Clentiazem  
25 Maleate; Detirelix Acetate; Devazepide; Donetidine; Etintidine Hydrochloride ; Famotidine;  
Fenmetozole Hydrochloride ; Flumazenil; Icatibant Acetate; Icotidine; Isradipine; Metiamide;  
Nadide; Nalmefene; Nalmexone Hydrochloride ; Naloxone Hydrochloride; Naltrexone; Nilvadipine;  
Oxilorphan; Oxmetidine Hydrochloride ; Oxmetidine Mesylate ; Quadazocine Mesylate; Ranitidine;  
Ranitidine Bismuth Citrate ; Ranitidine Hydrochloride ; Sufotidine; Teludipine Hydrochloride;  
30 Tiapamil Hydrochloride; Tiotidine; Vapiprost Hydrochloride; Zaltidine Hydrochloride.

Anterior pituitary activator: Epimestrol.

Anterior pituitary suppressant: Danazol.

Anthelmintic: Albendazole; Anthelmycin; Bromoxanide; Bunamidine Hydrochloride; Butonate; Cambendazole; Carbantel Lauryl Sulfate; Clioxyline; Closantel; Cyclobendazole; Dichlorvos; 5 Diethylcarbamazine Citrate; Dribendazole; Dymanthine Hydrochloride; Etibendazole; Fenbendazole; Furodazole; Hexylresorcinol; Mebendazole; Morantel Tartrate; Niclosamide; Nitramisole Hydrochloride; Nitroban; Oxantel Pamoate; Oxfendazole; Oxibendazole; Parbendazole; Piperamide Maleate; Piperazine; Piperazine Citrate; Piperazine Eddate Calcium; Proclonol; Pyrantel Pamoate; Pyrantel Tartrate; Pyrvium Pamoate; Rafoxanide; Stilbazium Iodide; Tetramisole 10 Hydrochloride; Thiabendazole; Ticarbazine; Tioxidazole; Triclofenol Piperazine; Vincosof; Zilan.

Anti-acne: Adapalene; Erythromycin Salnacelin; Inocoterone Acetate.

Anti-adrenergic: Acebutolol; Alprenolol Hydrochloride; Atenolol; Bretylium Tosylate; Bunolol 15 Hydrochloride; Carteolol Hydrochloride; Celiprolol Hydrochloride; Cetamolol Hydrochloride; Cicloprolol Hydrochloride; Dexopropranolol Hydrochloride; Diacetolol Hydrochloride; Dihydroergotamine Mesylate; Dilosalol Hydrochloride; Esmolol Hydrochloride; Exaproterenol Hydrochloride; Fenspiride Hydrochloride; Flestolol Sulfate; Labetalol Hydrochloride ; Levobetaxolol Hydrochloride; Levobunolol Hydrochloride; Metolol Hydrochloride; Metoprolol; 20 Metoprolol Tartrate; Nadolol; Pamatolol Sulfate; Penbutolol Sulfate; Phentolamine Mesylate; Practolol; Propranolol Hydrochloride; Proroxan Hydrochloride; Solypertine Tartrate; Sotalol Hydrochloride; Timolol; Timolol Maleate; Tiprenolol Hydrochloride; Tolamolol; Zolertine Hydrochloride.

25 Anti-allergic: Amlexanox; Astemizole; Azclastine Hydrochloride; Eclazolast ; Minocromil ; Nedocromil ; Nedocromil Calcium ; Nedocromil Sodium ; Nivimedone Sodium; Pemirolast Potassium ; Pentigetide; Pirquinozol; Poisonoak Extract; Probicromil Calcium; Proxicromil; Repirinast ; Tetrazolast Meglumine; Thiazinamium Chloride; Tiacrilast; Tiacrilast Sodium; Tiprinast Meglumine; Tixanox.

30

Anti-amebic : Berythromycin ; Bialamicol Hydrochloride; Chloroquine; Chloroquine Hydrochloride; Chloroquine Phosphate ; Clamoxyquin Hydrochloride; Clioquinol ; Emetine Hydrochloride;

Iodoquinol; Paromomycin Sulfate; Quinfamide; Symetine Hydrochloride; Teclozan; Tetracycline; Tetracycline Hydrochloride.

Anti-androgen: Benorterone; Cioteroncl; Cyproterone Acetate; Delmadinone Acetate ; Oxendolone;

5 Topterone; Zanoterone.

Anti-anemic: Epoetin Alfa; Epoetin Beta ; Ferrous Sulfate, Dried; Leucovorin Calcium.

Anti-anginal: Amlodipine Besylate; Amlodipine Maleate; Betaxolol Hydrochloride ; Bevantolol

10 Hydrochloride ; Butoprozine Hydrochloride; Carvedilol ; Cinepazet Maleate; Metoprolol Succinate ; Molsidomine ; Monatepil Maleate; Primadolol ; Ranolazine Hydrochloride; Tosifen; Verapamil Hydrochloride.

Anti-anxiety agent: Adatanserin Hydrochloride; Alpidem; Binospirone Mesylate; Bretazenil;

15 Glemanserin; Ipsapirone Hydrochloride; Mirisetron Maleate; Ocinaplon; Ondansetron Hydrochloride ; Panadiplon; Pancopride ; Pazinaclone; Serazapinc Hydrochloride; Tandospironc Citrate; Zalospirone Hydrochloride.

Anti-arthritis: Lodelaben .

20 Anti-asthmatic: Ablukast; Ablukast Sodium; Azelastine Hydrochloride : Bunaprolast; Cinalukast; Cromitrite Sodium; Cromolyn Sodium; Enofelast; Isamoxole; Ketotifen Fumarate; Levocromakalim; Lodoxamide Ethyl ; Lodoxamide Tromethamine; Montelukast Sodium; Ontazolast; Oxarbazole; Oxatomide; Piriprost; Piriprost Potassium; Pirolate; Pobilukast Edamine; Quazolast ; Repirinast; Ritolukast; Sulukast; Tetrazolast Meglumine ; Tiaramide Hydrochloride; Tibenelast Sodium; 25 Tomelukast; Tranilast; Verlukast; Veroxyline ; Zarirlukast.

Anti-atherosclerotic: Misobate; Timesurone.

Antibacterial: Acedapsone; Acetosulfone Sodium; Alamecin; Alexidine; Amdinocillin; Amdinocillin

30 Pivoxil; Amicycline; Amifloxacin; Amifloxacin Mesylate; Amikacin; Amikacin Sulfate; Aminosalicylic acid; Aminosalicylate sodium; Amoxicillin; Amphomycin; Ampicillin; Ampicillin Sodium; Apalcillin Sodium; Apramycin; Aspartocin; Astromicin Sulfate; Avilamycin; Avoparcin;

Azithromycin; Azlocillin; Azlocillin Sodium; Bacampicillin Hydrochloride; Bacitracin; Bacitracin Methylene Disalicylate; Bacitracin Zinc; Bambermycins; Benzoylpas Calcium; Berythromycin ; Betamicin Sulfate; Biapenem; Biniramycin; Biphenamine Hydrochloride ; Bispyritione Magsulfex; Butikacin; Butirosin Sulfate; Capreomycin Sulfate; Carbadox; Carbenicillin Disodium; Carbenicillin 5 Indanyl Sodium; Carbenicillin Phenyl Sodium; Carbenicillin Potassium; Carumonam Sodium; Cefaclor; Cefadroxil; Cefamandole; Cefamandole Nafate; Cefamandole Sodium; Cefaparole; Cefatrizine; Cefazaflur Sodium; Cefazolin; Cefazolin Sodium; Cefbuperazone; Cefdinir; Cefepime; Cefepime Hydrochloride; Cefetecol; Cefixime; Cefmenoxime Hydrochloride; Cefmetazole; Cefmetazole Sodium; Cefonicid Monosodium; Cefonicid Sodium; Cefoperazone Sodium; 10 Ceforanide; Cefotaxime Sodium; Cefotetan; Cefotetan Disodium; Cefotiam Hydrochloride; Cefoxitin; Cefoxitin Sodium; Cefpimizole; Cefpimizole Sodium; Cefpiramide; Cefpiramide Sodium; Cefpirome Sulfate; Cefpodoxime Proxetil; Cefprozil; Cefroxadine; Cefsulodin Sodium; Ceftazidime; Ceftibuten; Ceftizoxime Sodium; Ceftriaxone Sodium; Cefuroxime; Cefuroxime Axetil; Cefuroxime Pivoxetil; Cefuroxime Sodium; Cephacetrile Sodium; Cephalexin; Cephalexin Hydrochloride; 15 Cephaloglycin; Cephaloridine; Cephalothin Sodium; Cephapirin Sodium; Cephradine; Cetocycline Hydrochloride; Cetophenicol; Chloramphenicol; Chloramphenicol Palmitate; Chloramphenicol Pantothenate Complex ; Chloramphenicol Sodium Succinate; Chlorhexidine Phosphanilate; Chlóroxylon; Chlortetracycline Bisulfate; Chlortetracycline Hydrochloride; Cinoxacin; Ciprofloxacin; Ciprofloxacin Hydrochloride; Cirolemycin ; Clarithromycin; Clinafloxacin 20 Hydrochloride; Clindamycin; Clindamycin Hydrochloride; Clindamycin Palmitate Hydrochloride; Clindamycin Phosphate; Closazimine ; Cloxacillin Benzathine; Cloxacillin Sodium; Cloxyquin; Colistimethate Sodium; Colistin Sulfate; Coumermycin; Coumermycin Sodium; Cyclacillin; Cycloserine; Dalfopristin; Dapsone ; Daptomycin; Demeclocycline; Demeclocycline Hydrochloride; Demecycline; Denofungin ; Diaveridine; Dicloxacillin; Dicloxacillin Sodium; Dihydrostreptomycin 25 Sulfate; Dipyrithione; Dirithromycin; Doxycycline; Doxycycline Calcium : Doxycycline Fosfate; Doxycycline Hyclate; Droxacin Sodium; Enoxacin; Epicillin; Epitetracycline Hydrochloride; Erythromycin; Erythromycin Acistrate; Erythromycin Estolate; Erythromycin Ethylsuccinate; Erythromycin Gluceptate; Erythromycin Lactobionate; Erythromycin Propionate; Erythromycin Stearate; Ethambutol Hydrochloride; Ethionamide; Fleroxacin; Floxacillin; Fludalanine; 30 Flumequine; Fosfomycin; Fosfomycin Tromethamine; Fumoxicillin; Furazolium Chloride; Furazolium Tartrate; Fusidate Sodium; Fusidic Acid; Gentamicin Sulfate; Gloximonam; Gramicidin; Haloprogin; Hetacillin; Hetacillin Potassium; Hexedine; Ibasloxacin; Imipenem; Isoconazole;

Isepamicin; Isoniazid; Josamycin; Kanamycin Sulfate; Kitasamycin; Levofuraltadone; Levopropylcillin Potassium; Lexithromycin; Lincomycin; Lincomycin Hydrochloride; Lomefloxacin; Lomefloxacin Hydrochloride; Lomefloxacin Mesylate; Loracarbef; Mafenide; Meclocycline; Meclocycline Sulfosalicylate; Megalomicin Potassium Phosphate; Mequidox;

5 Meropenem; Methacycline; Methacycline Hydrochloride; Methenamine; Methenamine Hippurate; Methenamine Mandelate; Methicillin Sodium; Metioprim; Metronidazole Hydrochloride; Metronidazole Phosphate; Mezlocillin; Mezlocillin Sodium; Minocycline; Minocycline Hydrochloride; Mirincamycin Hydrochloride; Monensin; Monensin Sodium; Nafcillin Sodium; Nalidixate Sodium; Nalidixic Acid; Natamycin; Nebramycin; Neomycin Palmitate; Neomycin

10 Sulfate; Neomycin Undecylenate; Netilmicin Sulfate; Neutramycin; Nifuradene; Nifuraldezone; Nifuratel; Nifuratrone; Nisurdazil; Nifurimide; Nisurpirinol; Nifurquinazol; Nifurthiazole; Nitrocycline; Nitrofurantoin; Nitromide; Norfloxacin; Novobiocin Sodium; Ofloxacin; Ormetoprim; Oxacillin Sodium; Oximonam; Oximonam Sodium; Oxolinic Acid; Oxytetracycline; Oxytetracycline Calcium; Oxytetracycline Hydrochloride; Paldimycin; Parachlorophenol;

15 Paulomycin; Pefloxacin; Pefloxacin Mesylate; Penamecillin; Penicillin G Benzathine; Penicillin G Potassium; Penicillin G Procaine; Penicillin G Sodium; Penicillin V; Penicillin V Benzathine; Penicillin V Hydrabamine; Penicillin V Potassium; Pentizidone Sodium; Phenyl Aminosalicylate; Piperacillin Sodium; Pirbenicillin Sodium; Piridicillin Sodium; Pirlimycin Hydrochloride; Pivampicillin Hydrochloride; Pivampicillin Pamoate; Pivampicillin Probenate; Polymyxin B Sulfate;

20 Porfiromycin; Propikacin; Pyrazinamide; Pyrithione Zinc; Quinidecamine Acetate; Quinupristin; Racphenicol; Ramoplanin; Ranimycin; Relomycin; Repromicin; Risabutin; Rifametane; Rifamexil; Rifamide; Risampin; Risapentine; Rifaximin; Rolitetracycline; Rolitetracycline Nitrate; Rosaramicin; Rosaramicin Butyrate; Rosaramicin Propionate; Rosaramicin Sodium Phosphate; Rosaramicin Stearate; Rosoxacin; Roxarsone; Roxithromycin; Sancycline; Sanfetrinem Sodium;

25 Sarmoxicillin; Sarpicillin; Scopafungin; Sisomicin; Sisomicin Sulfate; Sparfloxacin; Spectinomycin Hydrochloride; Spiramycin; Stallimycin Hydrochloride; Steffimycin; Streptomycin Sulfate; Streptonicozid; Sulfabenz; Sulfabenzamide; Sulfacetamide; Sulfacetamide Sodium; Sulfacytine; Sulfadiazine; Sulfadiazine Sodium; Sulfadoxine; Sulfalene; Sulfamerazine; Sulfameter; Sulfamethazine; Sulfamethizole; Sulfamethoxazole; Sulfamonometroxine; Sulfamoxole; Sulfanilate

30 Zinc; Sulfanitran; Sulfasalazine; Sulfasomizole; Sulfathiazole; Sulfazamet; Sulfisoxazole; Sulfisoxazole Acetyl; Sulfisoxazole Diolamine; Sulfomyxin; Sulopenem; Sultamicillin; Suncillin Sodium; Talampicillin Hydrochloride; Teicoplanin; Temafloxacin Hydrochloride; Temocillin;

Tetracycline; Tetracycline Hydrochloride ; Tetracycline Phosphate Complex; Tetroxoprim;  
Thiamphenicol; Thiphencillin Potassium; Ticarcillin Cresyl Sodium; Ticarcillin Disodium;  
Ticarcillin Monosodium; Ticlatone; Tiodonium Chloride; Tobramycin; Tobramycin Sulfate;  
Tosufloxacin; Trimethoprim; Trimethoprim Sulfate; Trisulfapyrimidines; Troleandomycin;  
5 Trospectomycin Sulfate; Tyrothricin; Vancomycin; Vancomycin Hydrochloride; Virginiamycin;  
Zorbamycin.

Anticholelithic: Monoctanooin.

10 Anticholelithogenic: Chenodiol; Ursodiol.

Anticholinergic: Alverine Citrate; Anisotropine Methylbromide; Atropine; Atropine Oxide  
Hydrochloride; Atropine Sulfate; Belladonna; Benapryzine Hydrochloride; Benztetimide  
Hydrochloride; Benzilonium Bromide; Biperiden ; Biperiden Hydrochloride; Biperiden Lactate ;  
15 Clidinium Bromide; Cyclopentolate Hydrochloride; Dexetimide; Dicyclomine Hydrochloride;  
Dihexyverine Hydrochloride; Domazoline Fumarate; Elantrine; Elucaine; Ethybenztrapine;  
Eucatropine Hydrochloride; Glycopyrrolate; Heteronium Bromide; Homatropine Hydrobromide;  
Homatropine Methylbromide; Hyoscyamine; Hyoscyamine Hydrobromide; Hyoscyamine Sulfate;  
Isopropamide Iodide; Mepenzolate Bromide; Methylatropine Nitrate; Metoquazine; Oxybutynin  
20 Chloride; Parapenzolate Bromide; Pentapiperium Methylsulfate; Phencarbamide; Poldine  
Methylsulfate; Proglumide; Propantheline Bromide; Propenzolate Hydrochloride; Scopolamine  
Hydrobromide; Teimatroplium Methylsulfate; Tiquinamide Hydrochloride; Tosencacin Hydrochloride;  
Toquizinc; Triampyzine Sulfate; Trihexyphenidyl Hydrochloride; Tropicamide.

25 Anticoagulant: Ancrod; Anticoagulant Citrate Dextrose Solution ; Anticoagulant Citrate Phosphate  
Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Anticoagulant  
Heparin Solution; Anticoagulant Sodium Citrate Solution; Ardeparin Sodium; Bivalirudin ;  
Bromindione; Dalteparin Sodium ; Desirudin; Dicumarol; Heparin Calcium; Heparin Sodium;  
Lyapolate Sodium; Nafamostat Mesylate ; Phenprocoumon; Tinzaparin Sodium ; Warfarin Sodium.  
30 Anticoccidal: Maduramicin.

Anticonvulsant: Albutoin; Ameltolide; Atolide; Buramate; Carbamazepine ; Cinromide; Citenamide;

Clonazepam; Cyheptamide; Dezinamide; Dimethadione; Divalproex Sodium; Eterobarb; Ethosuximide; Ethotoin; Flurazepam Hydrochloride ; Fluzinamide; Fosphenytoin Sodium; Gabapentin; Ilepcimide; Lamotrigine; Magnesium Sulfate ; Mephenytoin; Mephobarbital ; Methetoin; Methylsuximide; Milacemide Hydrochloride ; Nabazenil; Nafimidone Hydrochloride;

5 Nitrazepam ; Phenacetamide; Phenobarbital ; Phenobarbital Sodium ; Phensuximide; Phenytoin; Phenytoin Sodium; Primidone; Progabide; Ralitoline; Remacemide Hydrochloride; Ropizine; Sabeluzole ; Stiripentol; Sulthiame; Thiopental Sodium ; Tiletamine Hydrochloride ; Topiramate; Trimethadione; Valproate Sodium; Valproic Acid; Vigabatrin; Zoniclezole Hydrochloride; Zonisamide.

10

Antidepressant: Adatanserin Hydrochloride; Adinazolam ; Adinazolam Mesylate; Alaproclate; Aletamine Hydrochloride; Amedalin Hydrochloride; Amitriptyline Hydrochloride; Amoxapine; Aptazapine Malcate; Azaloxan Fumarate; Azepindole; Azipramine Hydrochloride; Bipenamol Hydrochloride; Bupropion Hydrochloride; Butacetin; Butriptyline Hydrochloride; Caroxazone;

15 Cartazolate; Ciclazindol; Cidoxepin Hydrochloride; Cilobamine Mesylate; Clodazon Hydrochloride; Clomipramine Hydrochloride; Cotinine Fumarate; Cyclindole; Cypenamine Hydrochloride; Cyprolidol Hydrochloride; Cyproximide ; Daledalin Tosylate; Dapoxetine Hydrochloride; Dazadrol Maleate; Dazepinil Hydrochloride; Desipramine Hydrochloride; Dexamisole; Deximafen; Dibenzepin Hydrochloride; Dioxadrol Hydrochloride; Dothiepin Hydrochloride; Doxepin

20 Hydrochloride; Duloxetine Hydrochloride; Eclanamine Maleate; Encyprate; Etoperidone Hydrochloride; Fantridone Hydrochloride; Fenmetozole Hydrochloride ; Fenmetramide; Fezolamine Fumarate; Fluotracen Hydrochloride ; Fluoxetine; Fluoxetina Hydrochloride; Fluparoxan Hydrochloride; Gamfexine; Guanoxyfen Sulfate ; Imafen Hydrochloride; Imiloxan Hydrochloride; Imipramine Hydrochloride; Indeloxazine Hydrochloride; Intriptyline Hydrochloride; Iprindole;

25 Isocarboxazid; Ketipramine Fumarate; Lofepramine Hydrochloride; Lortalamine; Maprotiline; Maprotiline Hydrochloride; Melitracen Hydrochloride; Milacemide Hydrochloride; Minaprinc Hydrochloride; Mirtazapine; Moclobemide; Modaline Sulfate; Napactadine Hydrochloride; Napamezole Hydrochloride; Nefazodone Hydrochloride; Nisoxetine; Nitrafudam Hydrochloride; Nomifensine Maleate; Nortriptyline Hydrochloride; Octriptyline Phosphate; Opiplamol Hydrochloride; Oxaprotiline Hydrochloride; Oxpertine; Paroxetine; Phenelzine Sulfate; Pirandamine Hydrochloride; Pizotyline ; Prudefine Hydrochloride; Prolintane Hydrochloride; Protriptyline Hydrochloride; Quipazine Maleate ; Rolicyprine; Seproxetine Hydrochloride;

Sertraline Hydrochloride; Sibutramine Hydrochloride ; Sulpiride; Suritozole; Tametraline Hydrochloride; Tampramine Fumarate; Tandamine Hydrochloride; Thiazesim Hydrochloride; Thozalinone; Tomoxetine Hydrochloride; Trazodone Hydrochloride; Trebenzomine Hydrochloride; Trimipramine; Trimipramine Maleate; Venlafaxine Hydrochloride; Viloxazine Hydrochloride;

5 Zimeldine Hydrochloride; Zometapine.

Antidiabetic: Acetohexamide; Buformin; Butoxamine Hydrochloride ; Camiglibose; Chlorpropamide; Ciglitazone; Englitazone Sodium; Etoformin Hydrochloride; Gliamilide; Glibornuride; Glicetanile Sodium; Gliflumide; Glipizide; Glucagon; Glyburide; Glyhexamide;

10 Glymidine Sodium; Glyoctamide; Glyparamide; Insulin; Insulin, Dalanated; Insulin Human; Insulin Human, Isophane; Insulin Human Zinc; Insulin Human Zinc, Extended; Insulin, Isophane; Insulin Lispro; Insulin, Neutral; Insulin Zinc; Insulin Zinc, Extended; Insulin Zinc, Prompt; Linoglisiride; Linoglisiride Fumarate; Metformin; Methyl Palmostirate; Palmostirate Sodium; Pioglitazone Hydrochloride; Piroglisiride Tartrate; Proinsulin Human; Seglitide Acetate; Tolazamide; Tolbutamide;

15 Tolpyramide; Troglitazone; Zopolrestat.

Antidiarrheal: Rolgamicine, Diphenoxylate hydrochloride (Lomotil), Metronidazole (Flagyl), Methylprednisolone (Medrol), Sulfasalazine (Azulfidine).

20 Antidiuretic: Argipressin Tannate; Desmopressin Acetate; Lypressin .

Antidote: Dimercaprol; Edrophonium Chloride; Fomepizole; Leucovorin Calcium ; Levoleucovorin Calcium; Methylene Blue ; Protamine Sulfate.

Antidyskinetic: Selegiline Hydrochloride .

25 Anti-emetic: Alosetron Hydrochloride; Batanopride Hydrochloride; Bemesetron; Benzquinamide; Chlorpromazine ; Chlorpromazine Hydrochloride ; Clebopride; Cyclizine Hydrochloride; Dimenhydrinate; Diphenidol; Diphenidol Hydrochloride; Diphenidol Pamoate; Dolasetron Mesylate ; Domperidone; Dronabinol; Fludorex; Flumeridone; Galdansetron Hydrochloride; Granisetron;

30 Granisetron Hydrochloride; Lurosetron Mesylate; Meclizine Hydrochloride; Metoclopramide Hydrochloride; Metopimazine; Ondansetron Hydrochloride ; Pancopride; Prochlorperazine; Prochlorperazine Edisylate; Prochlorperazine Maleate ; Promethazine Hydrochloride ;

- 30 -

Thiethylperazine; Thiethylperazine Malate; Thiethylperazine Maleate; Trimethobenzamide Hydrochloride; Zocapride Hydrochloride.

Anti-epileptic: Felbamate; Lorcetazole; Tolgabide.

5

Anti-estrogen: Clometherone; Delmadinone Acetate ; Nafoxidine Hydrochloride; Nitromifene Citrate; Raloxifene Hydrochloride; Tamoxifen Citrate; Toremifene Citrate ; Trioxifene Mesylate.

Antifibrinolytic: Nafamostat Mesylate .

10

Antifungal: Acrisorcin; Ambruticin; Amphotericin B; Azaconazole; Azaserine; Basifungin; Bifonazole; Biphenamine Hydrochloride ; Bispyritione Magsulfex ; Butoconazole Nitrate; Calcium Undecylenate; Candicidin; Carbol-Fuchsin; Chlordantoin; Ciclopirox; Ciclopirox Olamine; Cilofungin; Cisconazole; Clotrimazole; Cuprimyxin; Denofungin ; Dipyrrithione; Doconazole;

15 Econazole; Econazole Nitrate; Enilconazole; Ethonam Nitrate; Fenticonazole Nitrate; Filipin; Fluconazole; Flucytosine; Fungimycin; Griseofulvin; Hamycin; Isoconazole ; Itraconazole; Kalafungin; Ketoconazole; Lomofungin; Lydimycin; Mepartycin ; Miconazole; Miconazole Nitrate; Monensin ; Monensin Sodium ; Naftifine Hydrochloride; Neomycin Undecylenate ; Nifuratel ; Nifurmerone; Nitralamine Hydrochloride; Nystatin; Octanoic Acid; Orconazole Nitrate; Oxiconazole

20 Nitrate; Oxifungin Hydrochloride; Parconazole Hydrochloride; Partricin ; Potassium Iodide ; Proclonol ; Pyritione Zinc ; Pyrrolnitrin; Rutamycin; Sanguinarium Chloride ; Saperconazole; Scopafungin ; Selenium Sulfide ; Sincfungin; Sulconazole Nitrate; Terbinafine; Terconazole; Thiram; Tiplatone ; Tioconazole; Tolciclate; Tolindate; Tolnaftate; Triacetin; Triafungin; Undecylenic Acid; Viridosulvin; Zinc Undecylenate; Zinoconazole Hydrochloride.

25

Antiglaucoma agent : Alprenoxime Hydrochloride ; Colforsin; Dapiprazole Hydrochloride ; Dipivefrin Hydrochloride ; Naboctate Hydrochloride ; Pilocarpine; Pirnabine.

Antihemophilic: Antihemophilic Factor.

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Antihemorrhagic: Poliglusam.

- 31 -

Antihistaminic: Acrivastine; Antazoline Phosphate; Astemizole; Azatadine Maleate; Barmastine; Bromodiphenhydramine Hydrochloride; Brompheniramine Maleate; Carboxamine Maleate; Cetirizine Hydrochloride; Chlorpheniramine Maleate; Chlorpheniramine Polistirex; Cinnarizine; Clemastine; Clemastine Fumarate; Closiramine Aceturate; Cyclramine Maleate; Cyclizine;

5 Cyproheptadine Hydrochloride; Dexbrompheniramine Maleate; Dexchlorpheniramine Maleate; Dimethindene Maleate; Diphenhydramine Citrate; Diphenhydramine Hydrochloride; Dorastine Hydrochloride; Doxylamine Succinate; Ebastine; Levocabastine Hydrochloride; Loratadine; Mianserin Hydrochloride; Nuberastine; Orphenadrine Citrate; Pyrabrom; Pyrilamine Maleate; Pyroxamine Maleate; Rocastine Hydrochloride; Rotoxamine; Tazifylline Hydrochloride;

10 Temelastine; Terfenadine; Tripelennamine Citrate; Tripelennamine Hydrochloride; Triprolidine Hydrochloride; Zolamine Hydrochloride.

Antihyperlipidemic: Cholestyramine Resin; Clofibrate; Colestipol Hydrochloride; Crilvastatin; Dalvastatin; Dextrothyroxine Sodium; Fluvastatin Sodium; Gemfibrozil; Lecimibide; Lovastatin; Niacin; Pravastatin Sodium; Probucol; Simvastatin; Tiqueside; Xenbucin.

15

Antihyperlipoproteinemic: Acifran; Beloxamide; Bezafibrate; Boxidine; Butoxamine Hydrochloride; Cetaben Sodium; Ciprofibrate; Gemcadiol; Halofenate; Lifibrate; Meglitol; Nafenopin; Pimetine Hydrochloride; Theofibrate; Tibric Acid; Treloxinate.

20 Antihypertensive: Alfuzosin Hydrochloride; Alipamide; Althiazide; Amiquinsin Hydrochloride; Amlodipine Besylate; Amlodipine Maleate; Anaritide Acetate; Atiprosin Maleate; Belfosdil; Bemiramide; Bendacalol Mesylate; Bendroflumethiazide; Benzthiazide; Betaxolol Hydrochloride; Bethanidine Sulfate; Bevantolol Hydrochloride; Biclodil Hydrochloride; Bisoprolol; Bisoprolol Fumarate; Bucindolol Hydrochloride; Bupicomide; Butthiazide; Candoxatril; Candoxatrilat; 25 Captopril; Carvedilol; Ceronapril; Chlorothiazide Sodium; Cicletanine; Cilazapril; Clonidine; Clonidine Hydrochloride; Clopamide; Cyclopenthiazide; Cyclothiazide; Darodipine; Debrisoquin Sulfate; Delapril Hydrochloride; Diapamide; Diazoxide; Dilevalol Hydrochloride; Diltiazem Malate; Ditekiren; Doxazosin Mesylate; Ecadotril; Enalapril Maleate; Enalaprilat; Enalkiren; Endralazine Mesylate; Epithiazide; Eprosartan; Eprosartan Mesylate; Fenoldopam Mesylate; 30 Flavodilol Maleate; Flordipine; Flosequinan; Fosinopril Sodium; Fosinoprilat; Guanabenz; Guanabenz Acetate; Guanacline Sulfate; Guanadrel Sulfate; Guancydine; Guanethidine Monosulfate; Guanethidine Sulfate; Guanfacine Hydrochloride; Guanisoquin Sulfate; Guanoclor

Sulfate; Guanoctine Hydrochloride; Guanoxabenz; Guanoxan Sulfate; Guanoxyfen Sulfate ;  
Hydralazine Hydrochloride; Hydralazine Polistirex; Hydroflumethiazide ; Indocrinone ; Indapamide  
; Indolapril Hydrochloride; Indoramin; Indoramin Hydrochloride; Indorenate Hydrochloride;  
Lacidipine; Leniquinsin; Levromakalim ; Lisinopril; Lofexidine Hydrochloride; Losartan  
5 Potassium; Losulazine Hydrochloride; Mebutamate; Mecamylamine Hydrochloride; Medroxalol;  
Medroxalol Hydrochloride; Methalothiazide ; Methyclothiazide ; Methyldopa; Methyldopate  
Hydrochloride; Metipranolol; Metolazone ; Metoprolol Fumarate; Metoprolol Succinate ;  
Metyrosine; Minoxidil ; Monatepil Maleate ; Muzolimine ; Nebivolol; Nitrendipine; Oformine;  
Pargyline Hydrochloride; Pazoxide; Pelanserin Hydrochloride ; Perindopril Erbumine;  
10 Phenoxybenzamine Hydrochloride; Pinacidil; Pivopril; Polythiazide ; Prazosin Hydrochloride;  
Primadol ; Prizidilol Hydrochloride; Quinapril Hydrochloride ; Quinaprilat ; Quinazosin  
Hydrochloride; Quinelorane Hydrochloride ; Quinpirole Hydrochloride; Quinuclium Bromide;  
Ramipril ; Rauwolfia Serpentina; Reserpine; Sapisartan Potassium; Saralasin Acetate; Sodium  
Nitroprusside; Sulfinalol Hydrochloride; Tasosartan; Teludipine Hydrochloride ; Temocapril  
15 Hydrochloride; Terazosin Hydrochloride; Terlakiren; Tiamenidine; Tiamenidine Hydrochloride;  
Ticrynafen ; TinabinoI; Tiodazosin; Tipentosin Hydrochloride; Trichlormethiazide ; Trimazosin  
Hydrochloride; Trimethaphan Camsylate; Trimoxamine Hydrochloride; Tripamide; Xipamide ;  
Zankiren Hydrochloride; Zofenoprilat Arginine.

20 Antihypotensive: Ciclafrine Hydrochloride; Midodrine Hydrochloride.

Anti-infective: Difloxacin Hydrochloride ; Lauryl Isoquinolinium Bromide; Moxalactam Disodium;  
Ornidazole; Pentisomycin; Sarafloxacin Hydrochloride; Protease inhibitors of HIV and other  
retroviruses; Integrase Inhibitors of HIV and other retroviruses; Cefaclor (Ceclor); Acyclovir  
25 (Zovirax); Norfloxacin (Noroxin); Cefoxitin (Mefoxin); Cefuroxime axetil (Ceftin); Ciprofloxacin  
(Cipro).

Anti-infective, topical: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride : Bithionolate  
Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride  
30 : Chlorhexidine Hydrochloride; Clioquinol ; Domiphen Bromide; Fentilor; Fludazonium Chloride;  
Fuchsin, Basic; Furazolidone ; Gentian Violet; Halquinols; Hexachlorophene: Hydrogen Peroxide;  
Ichthammol; Imidecyl Iodine; Iodine; Isopropyl Alcohol; Mafenide Acetate; Meralein Sodium;

Mercufenol Chloride; Mercury, Ammoniated; Methylbenzethonium Chloride; Nitrofurazone; Nitromersol; Octenidine Hydrochloride; Oxychlorosene; Oxychlorosene Sodium; Parachlorophenol, Camphorated; Potassium Permanganate; Povidone-Iodine; Sepazonium Chloride; Silver Nitrate; Sulfadiazine, Silver; Symclosene; Thimerfonate Sodium; Thimerosal : Troclosene Potassium.

5

Anti-inflammatory: Alclofenac; Alclometasone Dipropionate; Algestone Acetonide; Alpha Amylase;

Amcinafal; Amcinafide; Amfenac Sodium; Amiprilose Hydrochloride; Anakinra; Anirolac ;

Anitrazafen; Apazone; Balsalazide Disodium; Bendazac; Benoxaprofen ; Benzydamine

Hydrochloride; Bromelains; Broperamole; Budesonide; Carprofen; Cicloprofen; Cintazone;

10 Cliprofen; Clobetasol Propionate; Clobetasone Butyrate; Clopirac; Cloticasone Propionate;

Cormethasone Acetate; Cortodoxone; Deflazacort; Desonide; Desoximetasone; Dexamethasone

Dipropionate; Diclofenac Potassium; Diclofenac Sodium; Diflorasone Diacetate; Disflumidone

Sodium; Diflunisal ; Difluprednate; Diftalone; Dimethyl Sulfoxide; Drocinonide; Endrysone;

Enlimomab ; Enolicam Sodium ; Epirizole ; Etodolac; Etofenamate ; Felbinac; Fenamole; Fenbusen;

15 Fenclofenac; Fenclorac; Fendosal; Fenpipalone; Fentiazac; Flazalone; Fluazacort; Flufenamic Acid;

Flumizole; Flunisolide Acetate; Flunixin ; Flunixin Meglumine ; Fluocortin Butyl; Fluorometholone

Acetate; Fluquazone; Flurbiprofen ; Fluretofen; Fluticasone Propionate; Furaprofen; Eurobufen;

Halcinonide; Halobetasol Propionate; Halopredone Acetate; Ibufenac ; Ibuprofen; Ibuprofen

Aluminum; Ibuprofen Piconol; Ilonidap; Indomethacin; Indomethacin Sodium; Indoprofen ;

20 Indoxole ; Intrazole; Isoflupredone Acetate; Isoxepac; Isoxicam; Ketoprofen; Lofemizole

Hydrochloride ; Lornoxicam ; Loteprednol Etabonate; Meclofenamate Sodium; Meclofenamic Acid;

Meclorisone Dibutyrate; Mefenamic Acid ; Mesalamine; Meseclozone; Methylprednisolone

Suleptanate; Morniflumate; Nabumetone; Naproxen ; Naproxen Sodium ; Naproxol ; Nimazone;

Olsalazine Sodium; Orgotein ; Orpanoxin; Oxaprozin; Oxyphenbutazone; Paranyline Hydrochloride;

25 Pentosan Polysulfate Sodium; Phenbutazone Sodium Glycerate; Pirfenidone ; Piroxicam; Piroxicam

Cinnamate; Piroxicam Olamine; Pirprofen; Prednazate; Prifelone; Prodolic Acid; Proquazone;

Proxazole; Proxazole Citrate ; Rimexolone; Romazarit ; Salcolex ; Salnacedin; Salsalate ;

Sanguinarium Chloride ; Seclazone ; Sermetacin; Sudoxicam; Sulindac; Suprofen; Talmetacin;

Talinflumate ; Talosalate ; Tebuselone ; Tenidap; Tenidap Sodium; Tenoxicam; Tesicam; Tesimide;

30 Tetrydamine ; Tiopinac; Tixocortol Pivalate; Tolmetin; Tolmetin Sodium; Triclonide; Triflumidate;

Zidometacin; Zomepirac Sodium .

Antikeratinizing agent: Doretinol; Linarotene; Pelretin.

Antimalarial : Acetadapsone ; Amodiaquine Hydrochloride ; Amquinatc; Arteflene; Chloroquine ;

Chloroquine Hydrochloride ; Chloroquine Phosphate ; Cycloguanil Pamoate; Enpiroline Phosphate;

5 Halofantrine Hydrochloride ; Hydroxychloroquine Sulfate ; Mefloquine Hydrochloride; Menoctone; Mirincamycin Hydrochloride ; Primaquine Phosphate; Pyrimethamine; Quinine Sulfate; Tebuquine.

Antimicrobial: Aztreonam; Chlorhexidine Gluconate; Imidurea; Lycetamine; Nibroxane;

Pirazmonam Sodium; Propionic Acid ; Pyrithione Sodium; Sanguinarium Chloride ; Tigemonam

10 Dicholine.

Antimigraine: Dolasetron Mesylate ; Naratriptan Hydrochloride; Seroplexolc Maleate; Sumatriptan

Succinate; Zatosetron Maleate.

15 Antimitotic: Podofilox.

Antimycotic: Amorolfine.

Antinauscent : Buclizine Hydrochloride ; Cyclizine Lactate; Nabooctate Hydrochloride .

20

Antineoplastic: Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Aldesleukin ; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide ; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin ; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin

25 Sulfate; Brequinar Sodium; Broprimate ; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin ; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide ; Cytarabine ; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin

30 Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflornithine Hydrochloride ; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine

Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabinc; Fenretinide; Flouxuridine ; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198 ; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine;

5 Interferon Alfa-2a ; Interferon Alfa-2b ; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta-1 a ; Interferon Gamma-I b; Iproplatin; Irinotecan Hydrochloride ; Lanreotide Acetate; Letrozole; Leuprolide Acetate ; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate;

Melengestrol Acetate; Melphalan; Menogaril; Mercaptoperine; Methotrexate; Methotrexate Sodium;

10 Metoprine; Meturedopa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin ; Prednimustine; Procarbazine Hydrochloride; Puromycin ;

15 Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol ; Safingol Hydrochloride ; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprime; Thioguanine; Thiotepa; Tiazofurin;

20 Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredopa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin

25 Hydrochloride.

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecybenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G;

30 antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane;

atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; 5 budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxarnide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin 10 analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; daclizimab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dextrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; 15 droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemenc; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flazelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium 20 texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interseron agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; 25 irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellafin-N triacetate; lanreotide; lecinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide + estrogen + progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; 30 lovastatin; loxoribine; luritotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor;

mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A + mycobacterium cell wall sk; moperidol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone + pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; salingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiomustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin;

thymopoietin receptor agonist; thymotriptan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrophostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer.

Anti-cancer Supplementary Potentiating Agents: Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitryptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca<sup>++</sup> antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine); Amphotericin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and  
Multiple Drug Resistance reducing agents such as Cremaphor EL. The compounds of the invention also can be administered with cytokines such as granulocyte colony stimulating factor.

Antineutropenic: Filgrastim; Lenograstim; Molgramostim; Regramostim; Sargramostim.

Antiobsessional agent: Fluvoxamine Maleate.

Antiparasitic: Abamectin; Clorsulon; Ivermectin.

Antiparkinsonian: Benztropine Mesylate; Biperiden; Biperiden Hydrochloride; Biperiden Lactate; Carmantadine; Ciladopa Hydrochloride; Dopamine; Ethopropazine Hydrochloride; Lazabemide; Levodopa; Lometraline Hydrochloride; Mofegiline Hydrochloride; Naxagolide Hydrochloride; Pareptide Sulfate; Procyclidine Hydrochloride; Quinelorane Hydrochloride; Ropinirole Hydrochloride; Selegiline Hydrochloride; Tolcapone; Trihexyphenidyl Hydrochloride.

Antiperistaltic: Difenoximide Hydrochloride; Difenoxin; Diphenoxylate Hydrochloride; Fluperamide; Lidamidine Hydrochloride; Loperamide Hydrochloride; Malethamer; Nusfenoxole; Paregoric.

Antipneumocystic: Atovaquone.

Antiproliferative agent: Piritrexim Isethionate.

5 Antiprostatic hypertrophy: Sitogluside.

Antiprotozoal: Amodiaquine; Azanidazole; Bamnidazole; Carnidazole; Chlortetracycline Bisulfate ; Chlortetracycline Hydrochloride; Flubendazole; Flunidazole; Halofuginone Hydrobromide; Imidocarb Hydrochloride; Ipronidazole; Metronidazole; Misonidazole; Moxnidazole; Nitarsone;

10 Partricin; Puromycin; Puromycin Hydrochloride; Ronidazole; Sulnidazole; Tinidazole.

Antipruritic: Cyproheptadine Hydrochloride ; Methdilazinc; Methdilazinc Hydrochloride; Trimeprazine Tartrate.

15 Antipsoriatic: Acitretin; Anthralin; Azaribine; Calcipotriene; Cycloheximide; Enazadrem Phosphate; Etretinate; Liarozole Fumarate; Lonapalenc; Tepoxalin.

Antipsychotic: Acetophenazine Maleate; Alentemol Hydrobromide; Alpertine; Azaperone; Batelapine Maleate; Benperidol; Benzindopyrine Hydrochloride; Brofoxinc; Bromperidol; 20 Bromperidol Decanoate; Butaclamol Hydrochloride; Butaperazinc; Butaperazine Maleate; Carphenazine Maleate; Carvotroline Hydrochloride; Chlorpromazine; Chlorpromazine Hydrochloride; Chlorprothixene; Cinperene; Cintriamide; Clomacran Phosphate; Clopentixol; Clopimozide; Clopipazan Mesylate; Cloroperone Hydrochloride; Clothiapine; Clothixamide Maleate; Clozapine; Cyclophenazine Hydrochloride; Droperidol; Etazolate Hydrochloride; 25 Fenimide; Flucindole; Flumezapine; Fluphenazine Decanoate; Fluphenazine Enanthate; Fluphenazine Hydrochloride; Fluspiperone; Fluspirilene; Flutroline; Gevotroline Hydrochloride; Haloperidide; Haloperidol; Haloperidol Decanoate; Iloperidone; Imidoline Hydrochloride; Lenperone; Mazapertine Succinate; Mesoridazine; Mesoridazine Besylate; Metiapine; Milenperone; Milipertine; Molindone Hydrochloride; Naranol Hydrochloride; Neflumozide Hydrochloride; 30 Ocaperdone; Olanzapine; Oxiperomide; Penfluridol; Pentiapine Maleate; Perphenazine; Pimozide; Pinoxepin Hydrochloride; Pipamperone; Piperacetazine; Pipotiazine Palmitate; Piquindone Hydrochloride; Prochlorperazine Edisylate; Prochlorperazine Maleate; Promazine Hydrochloride;

Remoxipride; Remoxipride Hydrochloride; Rimcazole Hydrochloride; Seperidol Hydrochloride; Sertindole ; Setoperone; Spiperone; Thioridazine ; Thioridazine Hydrochloride; Thiothixene; Thiothixene Hydrochloride; Tioperidone Hydrochloride; Tiospirone Hydrochloride; Trifluoperazine Hydrochloride; Trifluperidol; Triflupromazine; Triflupromazine Hydrochloride; Ziprasidone  
5 Hydrochloride.

Antirheumatic: Auranofin; Aurothioglucose; Bindarit; Lobenzarit Sodium; Phenylbutazone; Pirazolac; Prinomide Tromethamine; Seprilose.

10 Antischistosomal: Beccanthonine Hydrochloride; Hycanthone; Lucanthone Hydrochloride; Niridazole; Oxamniquine; Pararosaniline Farnoate; Teroxalene Hydrochloride.

Antiseborrheic: Chloroxine; Piroctone; Piroctone Olamine; Resorcinol Monoacetate.

15 Antisecretory: Arbabrostil; Deprostil; Fenocimine Sulfate; Octreotide; Octreotide Acetate; Omeprazole Sodium; Rioprostil; Trimoprostil.

Anti-spasmodic: Stilonium Iodide; Tizanidine Hydrochloride.

20 Antithrombotic: Anagrelide Hydrochloride; Bivalirudin ; Dalteparin Sodium ; Danaparoid Sodium; Dazoxiben Hydrochloride; Efegatran Sulfate; Enoxaparin Sodium; Ifetroban; Ifetroban Sodium; Tinzaparin Sodium ; Trisenagrel.

25 Antitussive: Benzonatate; Butamirate Citrate; Chlophedianol Hydrochloride; Codeine Polistirex; Codoxime; Dextromethorphan; Dextromethorphan Hydrobromide; Dextromethorphan Polistirex; Ethyl Dibunate; Guaiapate; Hydrocodone Bitartrate; Hydrocodone Polistirex; Levoproxyphene Napsylate; Noscapine; Pemerid Nitrate; Pipazethate; Suxemerd Sulfate.

30 Anti-ulcerative: Aceglutamide Aluminum; Cadexomer Iodine ; Cetraxate Hydrochloride; Enisoprost; Isotiquimide; Lansoprazole; Lavoltidine Succinate; Misoprostol; Nizatidine; Nolinium Bromide ; Pantoprazole; Pifarnine; Pirenzepine Hydrochloride; Rabeprazole Sodium ; Remiprostol; Roxatidine Acetate Hydrochloride; Sucralfate; Sucrosofate Potassium; Tolimidone.

Anti-urolithic: Cysteamine; Cysteamine Hydrochloride; Tricitrates .

Antiviral: Acemannan; Acyclovir; Acyclovir Sodium; Adefovir; Alovudine; Alvircept Sudotox;  
Amantadine Hydrochloride; Aranotin; Arildone; Atevirdine Mesylate; Avridine; Cidofovir;  
5 Cipamfylline; Cytarabine Hydrochloride; Delavirdine Mesylate; Desciclovir; Didanosine; Disoxaril;  
Edoxudine; Enviradene; Enviroxime; Famciclovir; Famotine Hydrochloride; Fiacitabine;  
Fialuridine; Fosarilate; Foscarnet Sodium; Fosfonet Sodium; Ganciclovir; Ganciclovir Sodium;  
Idoxuridine; Kethoxal; Lamivudine; Lobucavir; Memantine Hydrochloride; Methisazone; Nevirapine;  
Penciclovir; Pirodavir; Ribavirin; Rimantadine Hydrochloride; Saquinavir Mesylate; Somantadine  
10 Hydrochloride; Sorivudine; Statolon; Stavudine; Tilorone Hydrochloride; Trifluridine; Valacyclovir  
Hydrochloride; Vidarabine; Vidarabine Phosphate; Vidarabine Sodium Phosphate; Viroxime;  
Zalcitabine; Zidovudine; Zinviroxime.

Appetite suppressant: Dexfenfluramine Hydrochloride; Phendimetrazine Tartrate; Phentermine  
15 Hydrochloride.

Benign prostatic hyperplasia therapy agent: Tamsulosin Hydrochloride.

Blood glucose regulators: Human insulin; Glucagon; Tolazamide; Tolbutamide; Chloropropamide;  
20 Acetohexamide and Glipizide.

Bone resorption inhibitor: Alendronate Sodium; Etidronate Disodium; Pamidronate Disodium.

Bronchodilator: Albuterol; Albuterol Sulfate; Azanator Maleate; Bamifylline Hydrochloride;  
25 Bitolterol Mesylate; Butaprost; Carbuterol Hydrochloride; Clorprenaline Hydrochloride; Colterol  
Mesylate; Doxaprost; Doxofylline; Dypphylline; Enprofylline; Ephedrine; Ephedrine Hydrochloride;  
Fenoterol; Fenprinast Hydrochloride; Guaihylline; Hexoprenaline Sulfate ; Hoquizil Hydrochloride;  
Ipratropium Bromide; Isoetharine; Isoetharine Hydrochloride; Isoetharine Mesylate; Isoproterenol  
Hydrochloride; Isoproterenol Sulfate; Metaproterenol Polistirex; Metaproterenol Sulfate; Nisbuterol  
30 Mesylate; Oxtrophylline; Picumeterol Fumarate; Piquizil Hydrochloride; Pirbuterol Acetate;  
Pirbuterol Hydrochloride; Procaterol Hydrochloride; Pseudocphedrine Sulfate; Quazodine ;  
Quinterenol Sulfate; Racpinephrine; Racpinephrine Hydrochloride; Reprotorol Hydrochloride;

Rimiterol Hydrobromide; Salmeterol; Salmeterol Xinafoate; Soterenol Hydrochloride; Sulfonterol Hydrochloride; Suloxifen Oxalate; Terbutaline Sulfate; Theophylline; Xanoxate Sodium; Zindotrine; Zinterol Hydrochloride.

5 Carbonic anhydrase inhibitor: Acetazolamide; Acetazolamide Sodium; Dichlorphenamide; Dorzolamide Hydrochloride; Methazolamide; Sezolamide Hydrochloride.

Cardiac depressant: Acecainide Hydrochloride; Acetylcholine Chloride; Actisomide; Adenosine; Amiodarone; Aprindine; Aprindine Hydrochloride; Artilide Fumarate; Azimilide Dihydrochloride;

10 Bidisomide; Bucainide Maleate; Bucromarone; Butoprozine Hydrochloride ; Capobenate Sodium; Capobenic Acid; Cifenline; Cifenline Succinate; Clofilium Phosphate; Disobutamide; Disopyramide; Disopyramide Phosphate; Dofetilide; Drobiline; Edisolone Acetate; Emilium Tosylate; Encainide Hydrochloride; Flecainide Acetate; Ibutilide Fumarate; Indecainide Hydrochloride; Ipazilide Fumarate; Lorajmine Hydrochloride; Lorcainide Hydrochloride; Meobentine Sulfate; Mexiletine  
15 Hydrochloride; Modecainide; Moricizine; Oxiramide; Pirmenol Hydrochloride; Pirolazamide; Pranolium Chloride; Procainamide Hydrochloride; Propafenone Hydrochloride; Pyrinoline; Quindonium Bromide; Quinidine Gluconate; Quinidine Sulfate; Recainam Hydrochloride; Recainam Tosylate; Risotilide Hydrochloride; Ropitoin Hydrochloride; Sematilide Hydrochloride; Suricainide Maleate; Tocainide; Tocainide Hydrochloride; Transcainide.

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Cardioprotectant: Dexrazoxane; Draflazine.

Cardiotonic: Actodigin; Amrinone; Bemoradan; Butopamine; Carbazcran; Carsatrin Succinate; Deslanoside; Digitalis; Digitoxin; Digoxin; Dobutamine; Dobutamine Hydrochloride; Dobutamine

25 Lactobionate; Dobutamine Tartrate; Enoximone; Imazodan Hydrochloride; Indolidan; Isomazole Hydrochloride; Levdobutamine Lactobionate; Lixazinone Sulfate; Medorinone; Milrinone; Pelrinone Hydrochloride; Pimobendan; Piroximone; Prinoxodan; Proscillaridin; Quazinone; Tazolol Hydrochloride; Vesnarinone.

30 Cardiovascular agent: Dopexamine; Dopexamine Hydrochloride.

Choleretic: Dehydrocholic Acid; Fencibutirol; Hymecromone; Piprozolin; Sincalide; Tocamphyl.

Cholinergic: Aceclidine; Bethanechol Chloride; Carbachol; Demecarium Bromide; Dexpanthenol; Echothiophate Iodide; Isoflurophate; Methacholine Chloride; Neostigmine Bromide; Neostigmine Methylsulfate; Physostigmine; Physostigmine Salicylate; Physostigmine Sulfate; Pilocarpine ; Pilocarpine Hydrochloride; Pilocarpine Nitrate; Pyridostigmine Bromide.

5

Cholinergic agonist: Xanomeline; Xanomeline Tartrate.

Cholinesterase Deactivator: Obidoxime Chloride; Pralidoxime Chloride; Pralidoxime Iodide; Pralidoxime Mesylate.

10

Coccidiostat: Arprinocid; Narasin ; Semduramicin; Semduramicin Sodium.

Cognition adjuvant: Ergoloid Mesylates; Piracetam; Pramiracetam Hydrochloride; Pramiracetam Sulfate; Tacrine Hydrochloride.

15

Cognition enhancer: Besipirdine Hydrochloride; Linopirdine; Sibopirdine .

Depressant: Omeprazole.

20 Diagnostic aid: Aminohippurate Sodium; Anazolene Sodium; Arclofenin; Arginine ; Bentiromide; Benzylpenicilloyl Polylysine; Butedronate Tetrasodium; Butifenin; Coccidioidin; Corticorelin Ovine Triflute ; Corticotropin, Repository ; Corticotropin Zinc Hydroxide; Diatrizoate Meglumine; Diatrizoate Sodium; Diatrizoic Acid; Diphtheria Toxin for Schick Test; Disofenin; Edrophonium Chloride; Ethiodized Oil; Etifenin; Exometazine; Ferristenc; Ferumoxides; Ferumoxsil; Fluorescein; 25 Fluorescein Sodium; Gadobenate Dimeglumine; Gadoteridol; Gadodiamide; Gadopentetate Dimegumine; Gadoversetamide; Histoplasmin; Impromidine Hydrochloride; Indigotindisulfonate Sodium; Indocyanine Green ; Iobenguane Sulfate I 123; Iobenzamic Acid; Iocarmate Meglumine; Iocarmic Acid; Iocetamic Acid; Iodamide; Iodamide Meglumine; Iodipamide Meglumine; Iodixanol; Iodoxamate Meglumine; Iodoxamic Acid; Ioglicic Acid; Ioglucol; Ioglucomide; Ioglycamic Acid; 30 Iogulamide; Iohexol; Iomeprol; Iopamidol; Iopanoic Acid; Iopentol; Iophendylate; Ioprofenin; Iopronic Acid; Ioproceamic Acid; Iopyadol; Iopydone; Iosfamic Acid; Ioseric Acid; Iosulamide Meglumine; Iosumetic Acid; Iotasul; Iotetric Acid; Iothalamate Meglumine; Iothalamate Sodium;

Iothalamic Acid; Iotrolan; Iotoxic Acid; Ioversol; Ioxaglate Meglumine; Ioxaglate Sodium; Ioxaglic Acid; Ioxilan; Ioxotrizoic Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps Skin Test Antigen; Pentetic Acid; Propyl iodone; Quinaldine Blue;

5 Schick Test Control; Sermorelin Acetate ; Sodium Iodide I-123; Sprodiamide; Stannous Pyrophosphate; Stannous Sulfur Colloid; Succimer; Teriparatide Acetate; Tetrofosmin; Tolbutamide Sodium; Tuberculin; Tyropanoate Sodium; Xylose.

Diuretic: Ambuphyline ; Ambuside; Amiloride Hydrochloride; Azolimine; Azosemide; Brocrinat;

10 Bumetanide; Chlorothiazide; Chlorthalidone; Clazolimine; Clorexolone; Ethacrynat Sodium; Ethacrynic Acid; Etozolin; Fenquizone; Furosemide; Hydrochlorothiazide; Isosorbide; Mannitol ; Mefruside; Ozolinone; Pirctanide; Spiroxasone; Torsemide; Triamterene; Triflocin; Urea.

Dopaminergic agent: Ibopamine.

15 Ectoparasiticide: Nifluridide; Permethrin.

Emetic: Apomorphine Hydrochloride.

20 Enzyme inhibitor: Acetohydroxamic Acid; Alrestatin Sodium; Aprotinin; Benazepril Hydrochloride; Benazeprilat; Benurestat; Bromocriptine; Bromocriptine Mesylate; Cilastatin Sodium; Flurosamide; Lergotrile; Lergotrile Mesylate; Levocycloserine; Libenzapril; Pentopril; Pepstatin; Perindopril; Polignate Sodium; Sodium Amylosulfate; Sorbinil; Spirapril Hydrochloride; Spiraprilat; Taleranol; Teprotide; Tolfamide; Zofenopril Calcium.

25 Estrogen: Chlorotrianisene; Dienestrol; Diethylstilbestrol; Diethylstilbestrol Diphosphate; Equilin; Estradiol; Estradiol Cypionate; Estradiol Enanthate; Estradiol Undecylate; Estradiol Valerate; Estrazinol Hydrobromide; Estriol; Estrofurate; Estrogens, Conjugated; Estrogens, Esterified; Estrone; Estropipate; Ethinyl Estradiol; Fenestrel; Mestranol; Nylestriol; Quinestrol.

30 Fibrinolytic: Anistreplase; Bisobrin Lactate; Brinolase.

Free oxygen radical scavenger: Pegorgotein.

Gastrointestinal Motility agents: Cisapride (Propulsid); Metoclopramide (Reglan); Hyoscyamine (Levsin).

Glucocorticoid: Amcinonide; Beclomethasone Dipropionate; Betamethasone; Betamethasone

5 Acetate; Betamethasone Benzoate; Betamethasone Dipropionate; Betamethasone Sodium Phosphate; Betamethasone Valerate; Carbenoxolone Sodium; Clocortolone Acetate; Clocortolone Pivalate; Cloprednol; Corticotropin; Corticotropin, Repository; Corticotropin Zinc Hydroxide; Cortisone Acetate; Cortivazol; Descinolone Acetonide; Dexamethasone; Dexamethasone Sodium Phosphate; Disflucortolone; Disflucortolone Pivalate; Flucloronide; Flumethasone; Flumethasone Pivalate; 10 Flunisolide; Fluocinolone Acetonide; Fluocinonide; Fluocortolone; Fluocortolone Caproate; Fluorometholone; Fluperolone Acetate; Fluprednisolone; Fluprednisolone Valerate; Flurandrenolide; Formocortal; Hydrocortisone; Hydrocortisone Acetate; Hydrocortisone Buteprate; Hydrocortisone Butyrate; Hydrocortisone Sodium Phosphate; Hydrocortisone Sodium Succinate; Hydrocortisone Valerate; Medrysone; Methylprednisolone; Methylprednisolone Acetate; Methylprednisolone 15 Sodium Phosphate; Methylprednisolone Sodium Succinate; Nivazol; Paramethasone Acetate; Prednicarbate; Prednisolone; Prednisolone Acetate; Prednisolone Hemisuccinate; Prednisolone Sodium Phosphate; Prednisolone Sodium Succinate; Prednisolone Tebutate; Prednisone; Prednival; Ticabesone Propionate; Tralonide; Triamcinolone; Triamcinolone Acetonide; Triamcinolone Acetonide Sodium; Triamcinolone Diacetate; Triamcinolone Hexacetonide.

20

Gonad-stimulating principle: Buserelin Acetate; Clomiphene Citrate; Ganirelix Acetate; Gonadorelin Acetate; Gonadorelin Hydrochloride; Gonadotropin, Chorionic; Menotropins.

Hair growth stimulant: Minoxidil .

25

Hemostatic: Aminocaproic Acid; Oxamatin Hydrochloride; Sulmarin; Thrombin; Tranexamic Acid.

Histamine H<sub>2</sub> receptor antagonists: Ranitidine (Zantac); Famotidine (Pepcid); Cimetidine (Tagamet); Nizatidine (Axid).

30

Hormone: Diethylstilbestrol; Progesterone; 17 hydroxy progesterone; Medroxyprogesterone; Norgestrel; Norethynodrel; Estradiol; Megestrol (Megace); Norethindrone; Levonorgestrel;

Ethyndiol; Ethinyl estradiol; Mestranol; Estrone; Equilin; 17 alpha dihydroequilin; equilenin; 17 alpha dihydroequilenin; 17 alpha estradiol; 17 beta estradiol; Leuprorelin (lupron); Glucagon; Testolactone; Clomiphene; Human menopausal gonadotropins; Human chorionic gonadotropin; Urofollitropin; Bromocriptine; Gonadorelin; Luteinizing hormone releasing hormone and analogs;

5 Gonadotropins; Danazol; Testosterone; Dihydroepiandrosterone; Androstenedione; Dihydrotestosterone; Relaxin; Oxytocin; Vasopressin; Folliculostatin; Follicle regulatory protein; Gonadoctrinins; Oocyte maturation inhibitor; Insulin growth factor; Follicle Stimulating Hormone; Luteinizing hormone; Tamoxifen.; Corticorelin Ovine Triflutate; Cosyntropin; Metogest; Pituitary, Posterior; Seractide Acetate; Somalapor; Somatrem; Somatropin; Somenopor; Somidobove.

10

Hypocholesterolemic: Lifibrol.

Hypoglycemic: Darglitazone Sodium; Glimepiride.

Hypolipidemic: Azalanstat Dihydrochloride; Colestolone; Surfomer; Xenalipin.

15

Hypotensive: Viprostol.

HMGCoA reductase inhibitors: Lovastatin (Mevacor); Simvastatin (Zocor); Pravastatin (Pravachol); Fluvasatin (Lescol).

20

Immunizing agent: Antirabies Serum; Antivenin (*Latrodectus mactans*); Antivenin (*Micruurus Fulvius*); Antivenin (*Crotalidae*) Polyvalent; BCG Vaccine; Botulism Antitoxin; Cholera Vaccine; Diphtheria Antitoxin; Diphtheria Toxoid; Diphtheria Toxoid Adsorbed; Globulin, Immune; Hepatitis B Immune Globulin; Hepatitis B Virus Vaccine Inactivated; Influenza Virus Vaccine; Measles Virus

25 Vaccine Live; Meningococcal Polysaccharide Vaccine Group A; Meningococcal Polysaccharide Vaccine Group C; Mumps Virus Vaccine Live; Pertussis Immune Globulin; Pertussis Vaccine; Pertussis Vaccine Adsorbed; Plague Vaccine; Poliovirus Vaccine Inactivated; Poliovirus Vaccine Live Oral; Rabies Immune Globulin; Rabies Vaccine; Rh<sub>o</sub>(D) Immune Globulin; Rubella Virus Vaccine Live; Smallpox Vaccine; Tetanus Antitoxin; Tetanus Immune Globulin; Tetanus Toxoid; 30 Tetanus Toxoid Adsorbed; Typhoid Vaccine; Yellow Fever vaccine; Vaccinia Immune Globulin; Varicella-Zoster Immune Globulin.

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· Immunomodulator: Dimepranol Acedoben; Imiquimod; Interferon Beta-1b; Lisofylline; Mycophenolate Mofetil; Prazatide Copper Acetate.

5 Immunoregulator: Azarole; Fanetizole Mesylate; Frentizole; Oxamisole Hydrochloride; Ristianol Phosphate; Thymopentin; Tilomisole.

Immunostimulant: Loxoridine ; Teceleukin.

Immunosuppressant: Azathioprine; Azathioprine Sodium; Cyclosporine; Daltroban; Gusperimus Trihydrochloride; Sirolimus; Tacrolimus.

10

Impotence therapy adjunct: Delequamine Hydrochloride.

Inhibitor: Acarbose; Atorvastatin Calcium; Benserazide ; Brocresine; Carbidopa; Clavulanate Potassium; Dazmegrel; Docobenone; Epoprostenol; Epoprostenol Sodium; Eprostereide; Finasteride; 15 Flurbiprofen Sodium; Furegrelate Sodium; Lufironil; Miglitol; Orlistat; Pimagedine Hydrochloride; Pirmagrel; Ponalrestat; Ridogrel; Sulbactam Benzathine ; Sulbactam Pivoxil ; Sulbactam Sodium ; Suronacrine Maleate; Tazobactam; Tazobactam Sodium; Ticlopidine Hydrochloride; Tirilazad Mesylate; Tolrestat; Velnacrine Maleate; Zifrosilone; Zileuton.

20 Keratolytic: Alcloxa ; Aldioxa ; Benzoyl Peroxide; Dibenzothiophene; Etarotene; Isotretinoin; Motretinide; Picotrin Diolamine; Resorcinol; Resorcinol Monoacetate ; Salicylic Acid; Sumarotene; Tazarotene; Tetroquinone; Tretinoin.

LHRH agonist: Deslorelin; Goserelin; Histrelin; Lutrelin Acetate; Nafarelin Acetate.

25

Liver disorder treatment: Malotilate.

Luteolysin: Fenprostalene.

30 Memory adjuvant: Dimoxamine Hydrochloride; Ribaminol.

Mental performance enhancer: Aniracetam.

Mood regulator: Fengabinc.

Mucolytic: Acetylcysteine; Carbocysteine; Domiodol.

5 Mucosal Protective agents: Misoprostol (Cytotec).

Mydriatic: Berefrine.

Nasal decongestant: Nemazoline Hydrochloride; Pseudoephedrine Polistirex.

10

Neuroleptic: Duoperone Fumarate; Risperidone.

Neuromuscular blocking agent: Atracurium Besylate; Cisatracurium Besylate; Doxacurium Chloride; Gallamine Triethiodide; Metocurine Iodide; Mivacurium Chloride; Pancuronium Bromide;

15 Pipecuronium Bromide; Rocuronium Bromide; Succinylcholine Chloride; Tubocurarine Chloride; Vecuronium Bromide.

Neuroprotective: Dizocilpine Maleate.

20 NMDA antagonist: Selotel.

Non-hormonal sterol derivative: Pregnenolone Succinate.

Oxytocic: Carboprost; Carboprost Methyl; Carboprost Tromethamine; Dinoprost ; Dinoprost

25 Tromethamine ; Dinoprostone ; Ergonovine Maleate; Metheneprost ; Methylergonovine Maleate; Oxytocin; Sparteine Sulfate.

Plasminogen activator: Alteplase; Urokinase.

30 Platelet activating factor antagonist: Lexipafant.

Platelet aggregation inhibitor: Acadesine; Beraprost; Beraprost Sodium; Ciprostenol Calcium; Itazigrel; Lilarizine; Oxagrelate.

Post-stroke and post-head trauma treatment: Citicoline Sodium.

Potentiator: Pentostatin; Talopram Hydrochloride.

5 Progestin: Algestone Acetophenide; Amadinone Acetate; Anagestone Acetate; Chlormadinone Acetate; Cingestol; Clogestone Acetate; Clomegestone Acetate; Desogestrel; Dimethisterone; Dydrogesterone; Ethynodiol Diacetate; Etonogestrel; Flurogestone Acetate; Gestacalone; Gestodene; Gestonorone Caproate; Gestrinone; Haloprogesterone; Hydroxyprogesterone Caproate; Levonorgestrel; Lynestrenol; Medrogestone; Medroxyprogesterone Acetate; Methynodiol Diacetate;  
10 Norethindrone; Norethindrone Acetate; Norethynodrel; Norgestimate; Norgestomet; Norgestrel; Oxogestone Phenpropionate; Progesterone; Quingestanol Acetate; Quingestrone; Tigestol.

Prostaglandin: Cloprostenol Sodium; Fluprostenol Sodium; Gemeprost; Prostalene; Sulprostone.

15 Prostate growth inhibitor: Pentomone.

Prothyrotropin: Protirelin.

Psychotropic: Minaprine.

20

Pulmonary surface: Beractant; Colfosceril Palmitate.

Radioactive agent: Fibrinogen I 125 ; Fludeoxyglucose F 18 ; Fluorodopa F 18 ; Insulin I 125; Insulin I 131; Iobenguane I 123; Iodipamide Sodium I 131 ; Iodoantipyrine I 131 ; Iodocholesterol  
25 I 131 ; Iodohippurate Sodium I 123 ; Iodohippurate Sodium I 125 ; Iodohippurate Sodium I 131 ; Iodopyracet I 125 ; Iodopyracet I 131 ; Iofetamine Hydrochloride I 123 ; Iomethin I 125 ; Iomethin I 131 ; Iothalamate Sodium I 125 ; Iothalamate Sodium I 131 ; Iotyrosine I 131; Liothyronine I 125; Liothyronine I 131; Merisoprol Acetate Hg 197; Merisoprol Acetate Hg 203; Merisoprol Hg 197 ; Selenomethionine Sc 75 ; Technetium Tc 99m Antimony Trisulfide Colloid; Technetium Tc 99m  
30 Bicisate ; Technetium Tc 99m Disifenin ; Technetium Tc 99m Etidronate ; Technetium Tc 99m Exametazime ; Technetium Tc 99m Furfosmin ; Technetium Tc 99m Gluceptate ; Technetium Tc 99m Lidofenin ; Technetium Tc 99m Mebrofenin ; Technetium Tc 99m Medronate ; Technetium

Tc 99m Medronate Disodium; Technetium Tc 99m Mertiatide ; Technetium Tc 99m Oxidronate ;  
Technetium Tc 99m Pentetate; Technetium Tc 99m Pentetate Calcium Trisodium; Technetium Tc  
99m Sestamibi ; Technetium Tc 99m Siboroxime ; Technetium Tc 99m Succimer ; Technetium Tc  
99m Sulfur Colloid ; Technetium Tc 99m Teboroxime ; Technetium Tc 99m Tetrofosmin ;  
5 Technetium Tc 99m Tiatide; Thyroxine I 125; Thyroxine I 131; Tolpovidone I 131 ; Triolein I 125;  
Triolein I 131.

Regulator: Calcifediol; Calcitonin; Calcitriol; Clodronic Acid; Dihydrotachysterol; Etidronic Acid;  
Oxidronic Acid; Piridronate Sodium; Risedronate Sodium; Secalciferol.

10 Relaxant: Adiphenine Hydrochloride; Alcuronium Chloride; Aminophylline; Azumolene Sodium;  
Baclofen; Benzoctamine Hydrochloride; Carisoprodol; Chlorphenesin Carbamate; Chlorzoxazone;  
Cinflumide; Cinnamedrine; Clodanolene; Cyclobenzaprine Hydrochloride; Dantrolene; Dantrolene  
Sodium; Fenalamide; Fenyripol Hydrochloride; Fetoxylate Hydrochloride; Flavoxate Hydrochloride;  
15 Fletazepam; Flumetramide; Flurazepam Hydrochloride; Hexafluorenium Bromide; Isomylamine  
Hydrochloride; Lorbamate; Mebeverine Hydrochloride; Mesuprine Hydrochloride ; Metaxalone;  
Methocarbamol; Methixene Hydrochloride; Nafomine Malate; Nelezaprine Maleate; Papaverine  
Hydrochloride; Pipoxolan Hydrochloride; Quinctolate; Ritodrine; Ritodrine Hydrochloride;  
Rolodine; Theophylline Sodium Glycinate; Thiphénamil Hydrochloride; Xilobarn.

20 Repartitioning agent: Cimaterol.

Scabicide: Amitraz; Crotamiton.

25 Sclerosing agent: Ethanolamine Oleate; Morrhuate Sodium; Tribenoside.

Sedative: Propiomazine.

Sedative-hypnotic: Allobarbital; Alomid; Alprazolam; Amobarbital Sodium; Bentazepam;  
30 Brotizolam; Butabarbital; Butabarbital Sodium; Butalbital; Capuride; Carbocloral; Chloral Betaine;  
Chloral Hydrate; Chlordiazepoxide Hydrochloride; Cloperidone Hydrochloride; Clorethate;  
Cyprazepam; Dexclamol Hydrochloride; Diazepam; Dichloralphenazone; Estazolam; Ethchlorvynol;

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Etomidate; Fenobam; Flunitrazepam; Fosazepam; Glutethimide; Halazepam; Lormetazepam;  
Mecloqualone; Meprobamate; Methaqualone; Midaflur; Paraldehyde; Pentobarbital; Pentobarbital  
Sodium; Perlapine; Prazepam; Quazepam; Reclazepam; Roletamide; Secobarbital; Secobarbital  
Sodium; Suproclone; Thalidomide; Tracazolate; Trepipam Maleate; Triazolam; Tricetamide;  
5 Triclofos Sodium; Trimetozine; Uldazepam; Zaleplon; Zolazepam Hydrochloride; Zolpidem  
Tartrate.

Selective adenosine A<sub>1</sub> antagonist: Apaxifylline.

10 Serotonin antagonist: Altanserin Tartrate; Amesergide; Ketanserin; Ritanserin.

Serotonin inhibitor: Cinanserin Hydrochloride; Fenclonine; Fonazine Mesylate; Xylamidine  
Tosylate.

Serotonin receptor antagonist: Tropanserin Hydrochloride.

15

Steroid: Dexamethasone Acefurate; Mometasone Furoate.

Stimulant: Amfonelic Acid; Amphetamine Sulfate; Ampyzine Sulfate; Arbutamine Hydrochloride;  
20 Azabon; Caffeine; Ceruletide; Cerulétide Diethylamine; Cisapride; Dazopride Fumarate;  
Dextroamphetamine; Dextroamphetamine Sulfate; Disfluanine Hydrochloride; Dimesoline  
Hydrochloride; Doxapram Hydrochloride; Etryptamine Acetate; Ethamivan; Fenethylline  
Hydrochloride; Flubanilate Hydrochloride; Flurothyl; Histamine Phosphate; Indriline  
Hydrochloride; Mefexamide; Methamphetamine Hydrochloride; Methylphenidate Hydrochloride;  
25 Pemoline; Pyrovalerone Hydrochloride; Xamoterol; Xamoterol Fumarate.

Suppressant: Amflutizole; Colchicine; Tazofelone.

Symptomatic multiple sclerosis: Fampridine.

30

Synergist: Proadifen Hydrochloride.

Thyroid hormone: Levothyroxine Sodium; Liothyronine Sodium; Liotrix.

Thyroid inhibitor: Methimazole; Propylthiouracil.

5 Thyromimetic: Thyromedan Hydrochloride.

Tranquilizer: Bromazepam; Buspirone Hydrochloride; Chlordiazepoxide; Clazolam; Clobazam;  
Clorazepate Dipotassium; Clorazepate Monopotassium; Demoxepam; Dexmedetomidine;  
Enciprazine Hydrochloride; Gepirone Hydrochloride; Hydroxyphenamate; Hydroxyzine  
10 Hydrochloride; Hydroxyzine Pamoate; Ketazolam; Lorazepam; Lorazafone; Loxapine; Loxapine  
Succinate; Medazepam Hydrochloride; Nabilone; Nisobamate ; Oxazepam; Pentabamate;  
Pirenperone; Ripazepam; Rolipram; Sulazepam; Taciamine Hydrochloride; Temazepam;  
Triflubazam; Tybamate; Valnoctamide.

15 Amyotrophic lateral sclerosis agents: Riluzole.

Cerebral ischemia agents: Dextrorphan Hydrochloride.

Page's disease agents: Tiludronate Disodium.

20

Unstable angina agents: Tirofiban Hydrochloride.

Uricosuric: Benzbromarone; Iremazole; Probencid; Sulfinpyrazone.

25 Vasoconstrictor : Angiotensin Amide; Felypressin; Methysergide; Methysergide Maleate.

Vasodilator: Alprostadil; Azaclorzine Hydrochloride; Bamethan Sulfate; Bepridil Hydrochloride;  
Buterizine; Cetiedil Citrate; Chromonar Hydrochloride; Clonitrate; Diltiazem Hydrochloride;  
Dipyridamole; Droprenilamine; Erythrityl Tetranitrate; Felodipine; Flunarizine Hydrochloride;  
30 Fostedil; Hexobendine; Inositol Niacinate; Iproxamine Hydrochloride; Isosorbide Dinitrate;  
Isosorbide Mononitrate; Isoxsuprine Hydrochloride; Lidoslazine; Mesenidil; Mesenidil Fumarate;  
Mibepradil Dihydrochloride; Mioslazine Hydrochloride; Mixidine; Nafronyl Oxalate; Nicardipine

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Hydrochloride; Nicergoline; Nicorandil; Nicotinyl Alcohol; Nifedipine; Nimodipine; Nisoldipine; Oxfenicine; Oxprenolol Hydrochloride; Pentaerythritol Tetranitrate; Pentoxifylline; Pentrinitrol; Perhexiline Maleate; Pindolol; Pirsidomine; Prenylamine; Propatyl Nitrate; Suloctidil; Terodilane Hydrochloride; Tipropidil Hydrochloride; Tolazoline Hydrochloride; Xanthinol Niacinate.

5      **Vulnerary:** Allantoin.

Wound healing agent: Erofermin.

Xanthine oxidase inhibitor: Allopurinol; Oxypurinol

10

Other pharmaceutical agents include: 1-decylpyrrolidinone; 1-dodecylpyrrolidinone; 16-alpha fluoroestradiol; 16-epiestriol; 16alpha-gitoxin; 17alpha estradiol; 17beta estradiol; 1alpha-hydroxyvitamin D2; 2'-nor-cGMP; 20-epi-1,25 dihydroxyvitamin D3; 22-oxacalcitriol; 2CVV; 3-isobutyl GABA; 6-FUDCA; 7-methoxytacrine; abamectin; abanoquil; abecarnil; abiraterone; 15 acadesine; acamprosate; acarbose; aceclofenac; acemannan; acetomepregenol; acetyl-L-carnitine; acetylcysteine, N-; acetylmethadol; acifran; acipimox; acitemate; acitretin; aclarubicin; aclatonium; napadisilate; aconiazide; acrivastinet; adafenoxate; adapalene; adatanserin; adecyepenol; adefovir dipivoxil; adelmidrol; ademetionine; adinazolam; adiposin; adozelesin; adrafinil; alacepril; aladapcin; alaptide; albendazole; albolabrin; aldecalmycin; aldesleukin; alendronic acid; alentemol; 20 alfalcacidol; alfuzosin; alglycerase; alinastine; alosetron; alpha idosone; alprostadil; altretamine; altromycin B; ambamustine; amelometasone; amesergide; amezinium metilsulfate; amfetamone; amidox; amifloxacin; amifostine; amiadarone; amisulpride; amlexanox; amlodipine; amlodipine; ampiroxicam; amrinone; amrubicin; amsacrine; amylin; amythiamicin; anagrelide; anakinra; ananain; anaritide; anastrozole; andrographolide; anordrin; apadoline; apafant; apaxifylline; 25 aphidicolin glycinate; apraclonidine; aprosulate sodium; aptiganel; apurinic acid; aranidipine; arbekacin; arbidol; arbutamine; ardeparin sodium; arecatannin B1; argatroban; aripiprazol; arotinolol; asimadoline; aspalatone; asperfuran; aspoxicillin; astemizole; asulacrinc; atamestane; atenolol, S-; atevirdine; atosiban; atovaquone; atpenin B; atrimustine; atrinositol; auracobasidin A; azadirachtine; azasetron; azatyrosine; azelaic acid; azelastine; azelnidipine; azimilide; azithromycin; 30 azosemide; aztreonam; baccatin III; bacoside A; bacoside B; bactobolamine; balazipone; balhimycin; balofloxacin; balsalazide; bambuterol; baohuoside I; barnidipine; basifungin; batebulast; batimastat; beauvericin; becaplermin; becliconazole; befloxatone; belfosdil;

bellenamine; benflumetol; benidipine; benzisoxazole; benzochlorins; benzoidazoxan; benzoylstauroporine; benzotropine; bepridil; beractant; beraprost; berafenone; bertosamil; besipirdine; beta-alethine; betaclamycin B; betamipron; betaxolol; betulinic acid; bevantolol; bicalutamide; bifemelane; bimakalim; bimithil; binospirone; bioxalomycin alpha2; biriperone; bis-  
5 benzimidazole A; bis-benzimidazole B; bisantrene; bisaramil; bisaziridinylspermine; bisnafide; bisoprolol; bistramide D; bistramide K; bistratene A; boldine; bopindolol; brefeldin; breflate; brimonidine; bromfenac; bromperidol; bropirimine; bucindolol; budesonide; budipine; budotitane; bunaprolast; bunazosin; butenafine; buthionine sulfoximine; butixocort propionate; cadexomer iodine; calanolide A; calcipotriol; calphostin C; camonagrel; candesartan; candesartan cilexetil;  
10 candoxatril; candoxatrilat; capecitabine; capromab; capsaicin; captopril; carbazomycin C; carbetocin; carbovir; carboxamide-amino-triazole; carboxyamidotriazole; carboxymethylated beta-1,3-glucan; carperitide; carteolol; carumonam; carvedilol; carvotroline; carzelesin; castanospermine; cebacetam; cecropin B; cescapene pivoxil; cefdaloxime pentexil tosilate; cefdinir; cefditoren pivoxil; cefepime; cefetamet; cefetamet pivoxil; cefixime; cefluprenam; cefmetazole; cefminox;  
15 cefodizime; cefoselis; cefotetan; cefotiam; cefotiam hexetil; cefozopran; cefpimizole; cefpiramide; cefpirome; cefpodoxime proxetil; cefprozil; cefsulodin; cesteram; cestibuten; ceftriaxone; cefuroxime axetil; celastrol; celikalin; celiprolol; cepacidine A; cerclamine; cerivastatin; ceronapril; certoparin sodium; cetiedil; cetirizine; chloroorienticin A; chloroorienticin B; chloroquinoxaline sulfonamide; cibenzoline; cicaprost; ciclesonide; ciçletanine; cicloprolol;  
20 cidofovir; cilansetron; cilazapril; cilnidipine; cilobradine; cilostazol; cimetropium bromide; cinitapride; cinolazepam; cioteronel; ciprofibrate; ciprofloxacin; ciprostene; cis-porphyrin; cisapride; cisatracurium besilate; cistinexine; citalopram; citicoline; citreamycin alpha; cladribine; clarithromycin; clausenamide; clebopride; clinafloxacin; clobazam; clobetasone butyrate; clodronic acid; clomethiazole; clopidogrel; clotrimazole; colestimide; colfosceril palmitate; collismycin A;  
25 collismycin B; combretastatin A4; complestatin; conagenin; contignasterol; contortrostatin; cosalane; costatolide; cotinine; coumermycin A1; cucumariosid; curacin A; curdlan sulfate; curiosin; cyclazosin; cyclic IHPMP; cyclobenzaprine; cyclobut A; cyclobut G; cyclocapron; cycloplatam; cyclosin; cyclothialidine; cyclothiazomycin; cypemycin; cyproterone; cytarabine ocfosfate; cytochalasin B; dacliximab; dactimicin; daidzein; daidzin; dalfopristin; dalteparin sodium;  
30 danaparoid; daphnodorin A; dapiprazole; dapitant; darifenacin; darlucin A; darsidomine; ddUTP; decitabine; deseriprone; deflazacort; dehydrodideamin B; dehydroepiandrosterone; delapril; delcquamine; delfaprazine; delmopinol; delphinidin; deoxypyridinoline; deprodone; depsidomycin;

deramciclane; dermatan sulfate; desflurane; desirudin; deslorelin; desmopressin; desogestrel; desoxoamiodarone; detajmum bitartrate; dexifosfamide; dexketoprofen; dexloxiglumide; dexmedetomidine; dexpemedolac; dexrazoxane; dexsotalol; dextrin 2-sulphate; dexverapamil; dezinamide; dezocine; diaziquone; diclofenac digolil; diclofenac potassium; dicranin; didemnin B; 5 didox; dienogest; diethylhomospermine; diethylnorspermine; dihydrexidine; dihydro-5-azacytidine; dimethyl prostaglandin A1; dimethylhomospermine; dimiracetam; dioxamycin; diphenencyprone; diphenyl spiomustine; diprafenone; dipropynorspermine; dirithromycin; discodermolide; disulfiram; ditekiren; docarpamine; docosanol, 1-; dofetilide; dolasetron; domitroban; dopexamine; dorzolamide; dosmalfate; dotarizine; doxacurium chloride; doxazosin; doxifluridine; doxofylline; 10 draculin; draflazine; droloxfene; dronabinol; droperidone; drotaverine acephyllinate; droxicam; ebiratide; ebrotidine; ebselen; ecabapide; ecabet; ecadotril; ecdisteron; echicetin; echistatin; ecomustine; ecteinascidin 722; ecteinascidin 729; ecteinascidin 743; edaravone; edelfosine; edobacomb; edrecolomab; efegatran; cflornithine; efondipine; equalen; elcatonin; eletriptan; elgodipine; eliprodil; eltenac; emakalim; emedastine; emiglitate; emitefur; emotakin; enadoline 15 hydrochloride; enalapril; cnazadrem; cnglitazone; cnlimomab; enoxacin; enoxaparin sodium; enoximone; entacapone; enterostatin; epoprostenol; epoxymexrenone; epristeride; eprosartan; eptastigmine; erdosteine; ersentilide; erosfermin; erythritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; everninomicin; examorelin; exemestane; fadrozole; saciefsfungin; famciclovir; fampridine; santosarone; faropenem; 20 fasidotril; fasudil; fazarabine; fedotozine; felbamate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; sepradinol; serpisofate sodium; ferristene; ferriyan; ferumoxsil; sexofenadine; flavopiridol; flecainide; flerobuterol; fleroxacin; flesinoxan; flezelastine; flobufen; flomoxef; florfenicol; florifenine; flosatidil; fluasterone; fluconazole; fludarabine; flumazenil; flumecinol; flumequine; flunarizine; fluocalcitriol; fluorodaunorubicin hydrochloride; fluoxetine, 25 R-; fluoxetine, S-; fluparoxan; flupirtine; flurbiprofen axetil; flurithromycin; fluticasone propionate; flutrimazole; fluvastatin; fluvoxamine; forasartan; forsenimex; formestane; formoterol; formoterol, R,R-; fosfomycin; trometamol; fosinopril; fosphenytoin; fostriecin; sotemustine; gabapentin; gadobenic acid; gadobutrol; gadodiamide; gadodiamide-EOB-DTPA; gadolinium texaphyrin; gadoteric acid; gadoteridol; gadoversetamide; galantamine; galdansetron; gallopamil; galocitabine; 30 gamolenic acid; ganirelix; gepirone; gestrinone; girisopam; glaspimod; glaucocalyxin A; glutapyrone; glycopine; glycopril; granisetron; grepafloxacin; halichondrin B; halofantrine; halomon; halopredone; hatomamicin; hatomarubigin A; hatomarubigin B; hatomarubigin C;

hatomarubigin D; ibogaine; ibopamine; ibudilast; illimaquinone; ilmofosine; ilomastat; iloperidone; iloprost; imidapril; imidazenil; indinavir; indolidan; indometacin farnesil; indometacin; tropine ester; indoramin; inocoterone; inogatran; inolimomab; interferon alfa; interferon alfa-2a; interferon alfa-2b; interferon alfa-N1; interferon alfa-n3; interferon beta; interferon beta-1a; interferon beta-1b; 5 interferon gamma-1a; interferon gamma-1b; interferon omega; interferon, consensus; interleukin-1; interleukin-1 alpha; interleukin-1 beta; interleukin-10; interleukin-11; interleukin-12; interleukin-12; interleukin-15; interleukin-2; interleukin-3; interleukin-4; interleukin-5; interleukin-7; interleukin-8; iobenguane; iobitridol; iodoamiloride; iododoxorubicin; iofratol; iomeprol; iopentol; iopromide; iopyrol; iotriside; ioversol; ioxilan; ipazilide; IpdR; ipenoxyzone; ipidacrine; ipomeanol, 4-; 10 ipriflavone; ipsapirone; irbesartan; irinotecan; irloxacin; irsogladine; irtermazole; isalsteine; isbogrel; isepamicin; isobengazole; isofloxythepin; isohomohalicondrin B; isopropyl unoprostone; isradipine; itameline; itasetron; itopride; itraconazole; ketoprofen, R-; ketoprofen, S-; ketorolac; lacidipine; lactitol; lactic acid; laennec; lasutidine; lamellarin-N triacetate; lamifiban; lamivudine; lamotrigine; 15 lanconazole; lanperisone; lanreotide; lansoprazole; latanoprost; lateritin; laurocapram; lazabemide; lemelexacin; lemildipine; leminoprazole; lenercept; lenograstim; lentinan sulfate; leptin; leptolstatin; lercanidipine; lerisetron; lesopitron; letazuril; letrozole; leucomyzin; leuprorelin; levocromakalim; levetiracetam; levobetaxolol; levobunolol; levobupivacaine; levocabastine; levocarnitine; levodropizine; levofloxacin; levomoprolol; levonorgestrel; levormeloxifene; levosimendan; levosulpiride; linotroban; linsidomine; lintitript; lontopride; liothyronine sodium; 20 lircepride; lisinopril; lobaplatin; lobucavir; lodoxamide; lombricine; lomefloxacin; lomerizine; lometrexol; lonazolac; lonidamine; loracarbef; loratadine; lorglumide; lornoxicam; losartan; losigamone; losoxantrone; loteprednol; lovistatin; loxoribine; lubcluzole; lurtotecan; luteinizing hormone; lutetium; luzindole; lydicamycin; lysofylline; lysostaphin; magainin 2 amide; magnolol; mallotochromene; mallotojaponin; malotilate; mangafodipir; manidipine; maniwamycin A; 25 mannostatin A; manumycin E; manumycin F; mapinastine; marimastat; Martek 8708; Martek 92211; masoprolol; maspin; masetolide; meterelin; methoxatone; methylhistamine, R-alpha; methylinosine monophosphate; methylprednisolone aceponate; methylprednisolone suleptanate; metiparmide; metoclopramide; metoprolol, S-; metrifonate; mibepradil; michellamine B; microcolin A; midodrine; misepristone; miglitol; milacemide; milameline; mildronate; milnacipran; milrinone; 30 miltefosine; minaprine; miokamycin; mipragoside; mirsentanil; mirimostim; mirtazapine; misoprostol; mitoguazone; mitolactol; mitonafide; mitoxantrone; mivacurium chloride; mivazerol; mixanpril; mizolastine; mizoribine; moclobemide; modafinil; moexipril; mofarotene; moszolac;

molgramostim; mometasone; montirelin; mopidamol; moracizine; mosapramine; mosapride; motilide; moxiraprine; moxonidine; nadifloxacin; nadroparin calcium; nafadotride; nafamostat; nafarelin; naftopidil; naglivan; nagrestip; nalmesene; naphterpin; napsagatran; naratriptan; nartograstim; nasaruplase; nateplase; niperotidine; niravoline; nisamycin; nisin; nisoldipine;  
5 nitazoxanide; nitecapone; nitrendipine; nitrendipine, S-; nitrofurantoin monohydrate; nitrallyn; nizatidine; ofloxacin; okicenone; olanzapine; olopatadine; olprinone; olsalazine; omeprazole; onapristone; ondansetron; ondansetron, R-; ontazolast; oracin; otenezepad; oxaliplatin; oxamisole; oxandrolone; oxaprozin; oxaunomycin; oxcarbazepine; oxiconazole; oxiracetam; oxodipine; ozagrel; palauamine; palinavir; palmitoylrhizoxin; pamaqueside; pamicogrel; pamidronic acid; panamesine;  
10 panaxytriol; panipenem; panipenum; pannorin; panomifene; pantethine; pantoprazole; parabactin; parnaparin sodium; paroxetine; parthenolide; pazelliptine; pazufloxacin; pefloxacin; pegaspargase; peldesinc; pemedolac; pemirolast; penciclovir; pentafuside; pentamidine; pentamorphone; pentigetide; pentosan; pentostatin; pentrozole; perflubron; perfosfamide; pergolide; perindoprilat; perospirone; phenaridine; phenazinomycin; phenserine; phensuccinal; phentolamine mesilate;  
15 phenylacetate; phenylalanyl ketoconazole; picenadol; picibanil; picroliv; picumeterol; pidotimod; pilocarpine hydrochloride; pilsicainide; pimagedine; pimilprost; pimobendan; pinacidil; pinocebrin; pioglitazone; pipecuronium bromide; pirarubicin; piretanide; pirfenidone; piritrexim; pirlindole; pirmagrel; pirmenol; pirodavir; piromast; piroxicam cinnamate; propagermanium; propentofylline; propionylcarnitine, L-; propirani; propiram + paracetamol; propiverine; propyl bis-acridone;  
20 prostaglandin J2; prostratin; protegrin; protosufloxacin; prulifloxacin; pyrazoloacridine; quazepam; quetiapine; quiflapon; quinagolide; quinapril; quinsamide; quinupristin; raloxifene; raltitrexed; ramatroban; ramipril; ramosetron; ranelic acid; ranitidine bismuth citrate; ranolazine; recainam; regavirumab; relaxin; repirinast; resiniferatoxin; reticulon; reviparin sodium; revizinone; ricasetron; ridogrel; risabutin; risapentine; rifaximin; riopirox; riluzole; rimantadine; rimexolone; rimoprogyn;  
25 riodipine; ripisartan; risedronic acid; rispenzepine; risperidone; ritanserin; ritipenem; ritipenem acoxil; ritolukast; ritonavir; rizatriptan benzoate; rohitukine; rokitamycin; ropinirole; ropivacaine; roquinimex; roxatidine; roxindole; roxithromycin; rubiginone B1; ruboxyl; rufloxacin; rupatidine; ruzadolane; safingol; safironil; saintopin; salbutamol, R-; salmeterol; salmeterol, R-salnacedin; sameridine; sampatrilat; sansetrinem; saprisartan; sapropterin; saquinavir; SarCNU; sarcophytol A  
30 sargramostim; sarpogrelate; saruplase; saterinone; satigrel; satumomab pendetide; sclegiline; selenium thiosemicarbazone; sematilide; semduramicin; semotiadiil; semustine; sermorelin; sertaconazole; sertindole; sertraline; setiptiline; sevirumab; sevoflurane; sezolamide; silipide;

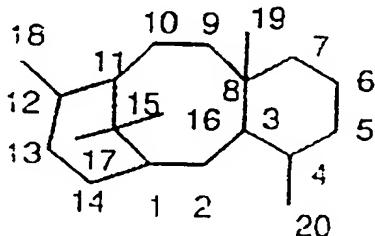
silteplase; simendan; simvastatin; sinitrodil; sinnabidol; sipatrigine; sirolimus; sizofiran; somatomedin B; somatomedin C; somatrem; somatropin; sonermin; sotalol; staurosporine; stavudine; stepronin; stipiamide; stiripentol; stobadine; succibun; sucralfate; sulfasalazine; sulfinosine; sulfoxamine; sulopenem; sultamicillin; sultopride; sulukast; sumatriptan; symakalim; 5 tandospirone; tapgen; taprostene; tasosartan; tazanolast; tazarotene; teicoplanin; telenzepine; tellurapyrylium; telmesteine; telmisartan; temocapril; temoporfin; temozolomide; tenidap; teniposide; tenosal; tenoxicam; tepirindole; tepoxalin; terazosin; terbinafine; terfenadine; terflavoxate; terguride; terlakiren; terlipressin; terodiline; tertatolol; testosterone bucinate; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thiofedrine; thiomarinol; 10 thioperamide; thyroid stimulating hormone; tiagabine; tianeptine; tiapafant; tibolone; ticlopidine; tienoxolol; tilisolol; tilnoprofen arbame; tiludronic acid; tinzaparin sodium; tiotropium bromide; tipredane; tiqeside; tirandalydigin; tirapazamine; tilazad; tirofiban; tiropramide; topsentin; torasemide; toremifene; tosusloxacin; trafermin; trandolapril; traxanox; tretinoin; tretinoin tocoferil; triacetyluridine; tricaprilin; trichohyalin; trichosanthin. alpha; triciribine; trientine; triflavin; 15 trimegestone; triptorelin; troglitazone; trombodipine; tropisetron; trospectomycin; trovafloxacin; trovirdine; tucaresol; tulobuterol; tylogenin; urapidil; uridine triphosphate; valaciclovir; valproate magnesium; valproate semisodium; valsartan; vamicamide; vanadeine; vaninolol; vapreotide; variolin B; velaresol; venlafaxine; veramine; verapamil, (S); verdins; veroxan; verteporfin; vesnarinone; vexibinol; vigabatrin; vinburnine citrate; vinburnine resinate; vinconate; vinorelbine; 20 vincristine; vinpocetine; vinpocetine citrate; vintoperol; vinxalting; voriconazole; vorozole; voxergolide; xemilofiban; ximoprofen; yangambin; zabiclopril; zacopride; zacopride, R-; zafirlukast; zalcitabine; zaleplon; zolospirone; zaltoperol; zanamivir; zankiren; zanoterone; zatebradine; zatosetron; zenarestat; zeniplatin; zifrosilone; zilascorb; zileuton; zinostatin stimalamer; ziprasidone; zoledronic acid; zolmitriptan; zolpidem; zonisamide; zopiclone; zopiclone, S-; zopolrestat; zotepine.

25 The invention also embraces novel compositions of matter that are covalent conjugates of DHA and pharmaceutical agents that are noncentral nervous system active agents. Noncentral nervous system active agents have no function or use within the central nervous system. Their only use is outside of the central nervous system. Such agents include all drugs within certain of the foregoing categories and only some drugs within other of the foregoing categories. For example, 30 the entire category of blood glucose regulators have no use or function within the central nervous system. In contrast, certain anti-cancer agents are useful in the central nervous system whereas others are not. For example, central nervous system cancers are not hormone dependent, and,

therefore, an anti-cancer agent such as Tamoxifen which treats certain hormone dependent cancers is not useful in the central nervous system. Those skilled in the art will be able to identify readily those categories and/or members of a category which are noncentral nervous system active agents. Among the foregoing compounds, the following categories and/or members of the following 5 categories are noncentral nervous system active agents: adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; amino acid; anabolic; androgen; antagonist; anthelmintic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-androgen; anti-anemic; anti-anginal; anti-arthritis; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholelithic; anticholelithogenic; anticholinergic; anticoagulant; anticoccidal; antidiabetic; antidiarrheal; 10 antidiuretic; antidote; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, topical; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimitotic; antimycotic, antineoplastic; antineutropenic, antiparasitic; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic; 15 hypertrophy; antiprotozoal; antipruritic; antipsoriatic; antirheumatic; antischistosomal; antiseborrheic; antisecretory; antispasmodic; antithrombotic; antitussive; anti-ulcerative; anti-urolithic; antiviral; appetite suppressant; benign prostatic hyperplasia therapy agent; bone resorption inhibitor; bronchodilator; carbonic anhydrase inhibitor; cardiac depressant; cardioprotectant; cardiotonic; cardiovascular agent; choleretic; cholinergic; cholinergic agonist; 20 cholinesterase deactivator; coccidiostat; diagnostic aid; diuretic; ectoparasiticide; enzyme inhibitor; estrogen; fibrinolytic; free oxygen radical scavenger; glucocorticoid; gonad-stimulating principle; hair growth stimulant; hemostatic; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; impotence therapy adjunct; inhibitor; keratolytic; LHRH agonist; liver disorder; 25 treatment; luteolin; mucolytic; mydriatic; nasal decongestant; neuromuscular blocking agent; non-hormonal sterol derivative; oxytocic; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; potentiator; progestin; prostaglandin; prostate growth inhibitor; prothyrotropin; pulmonary surface; radioactive agent; regulator; relaxant; repartitioning agent; scabicide; sclerosing agent; selective adenosine A<sub>1</sub> antagonist; steroid; suppressant; 30 symptomatic multiple sclerosis; synergist; thyroid hormone; thyroid inhibitor; thyromimetic; amyotrophic lateral sclerosis agents; Paget's disease agents; unstable angina agents; uricosuric; vasoconstrictor; vasodilator; vulnerary; wound healing agent; xanthine oxidase inhibitor.

As used herein, a taxane is a molecule that possesses the following tricyclic carbon-atom connectivity network, which may incorporate carbon-carbon multiple bonds, and which through the involvement of carbon-atom-noncarbon-atom bonds may include substituents, functional groups, and additional rings.

5



10 A taxoid is a molecule structurally related to a taxane in which the above taxane carbon-atom connectivity network is altered, for example, by cleavage of one or more of the carbocyclic rings, by deletion or addition of carbon substituents, by connection of carbon atoms normally not bonded to each other, by disconnection of carbon atoms normally bonded to each other, or by some other reorganization of or adjustment to the taxane carbon-atom connectivity network, but in which one 15 or more structural features characteristic of the taxane carbon-atom connectivity network are conserved.

The compounds useful in the invention may be delivered in the form of anti-cancer cocktails. An anti-cancer cocktail is a mixture of any one of the compounds useful with this invention with another anti-cancer agent such as an anti-cancer drug, a cytokine, and/or supplementary potentiating 20 agent(s). The use of cocktails in the treatment of cancer is routine. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, injectable solution, etc.) would contain both the conjugate useful in this invention and the anti-cancer drug and/or supplementary potentiating agent.

The compounds of the invention, when used in cocktails, are administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters 25 discussed below; but, in any event, is that amount which establishes a level of the drug(s) in the area of the tumor which is effective in inhibiting the tumor growth.

When administered, the formulations of the invention are applied in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other 30 therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such

pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be 5 prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and a salt (1-2% W/V); citric acid and a salt (1-3% W/V); boric acid and a salt (0.5-2.5% W/V); and phosphoric acid and a salt (0.8-2% W/V).

Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V).

10 The active compounds of the present invention may be a pharmaceutical composition having a therapeutically effective amount of a conjugate of the invention optionally included in a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid filler, dilutants or encapsulating substances which are suitable for administration to a human or other animal. The term "carrier" denotes an organic or 15 inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions are capable of being commingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

20 Compositions suitable for parenteral administration conveniently comprise a sterile preparation of the conjugates of the invention. This preparation may be formulated according to known methods. Formulations for taxanes can be found in Chapter 9 of Taxol: Science and Applications, CRC Press, Inc., 2000 Corporate Boulevard, N.W., Boca Raton, FL 33431. In general, Taxol has been formulated as a 6 mg/ml cremophor EL (polyoxyethylated castor oil)/ethanol mixture, which is diluted to final volume with normal saline or 5% dextrose. A 15mg/ml solution 25 of taxotere has been formulated in polysorbate 80 (polyoxycethylene sorbitanmonoooleate)/ethanol mixture, diluted with 5% dextrose.

30 The sterile preparation thus may be a sterile solution or suspension in a non-toxic parenterally-acceptable diluent or solvent. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Carrier formulations suitable for oral, subcutaneous, intravenous, intramuscular, etc. can be found in Remington's Pharmaceutical Sciences, Mack

Publishing Company, Easton, PA.

A subject as used herein means humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

The conjugates of the invention are administered in effective amounts. An effective amount means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of or diagnose the particular condition being treated. In general, an effective amount for treating cancer will be that amount necessary to inhibit mammalian cancer cell proliferation in-situ. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically.

Generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 1000 mg/kg per day. It is expected that IV doses in the range of about 1 to 1000 mg/m<sup>2</sup> per day will be effective. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous IV dosing over, for example 24 hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the conjugates of the invention into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately

bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the active compounds of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

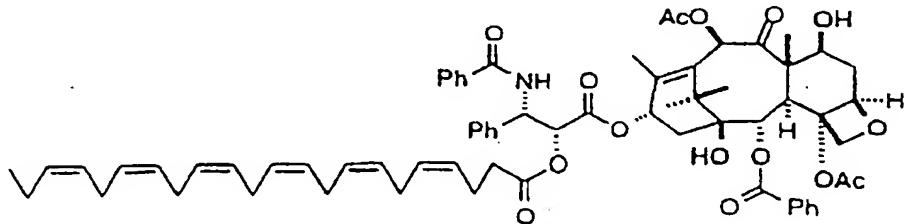
A long-term sustained release implant also may be used. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the compounds of the invention.

The conjugates of the invention also are useful, in general, for treating mammalian cell proliferative disorders other than cancer, including psoriasis, actinic keratosis, etc. They further are useful in treating diabetes and its complications, excess acid secretion, cardiovascular conditions involving cholesterol (e.g., hyperlipidemia and hypercholesterolemia), diarrhea, ovarian diseases (e.g. endometriosis, ovarian cysts, etc.) and as contraceptive agents.

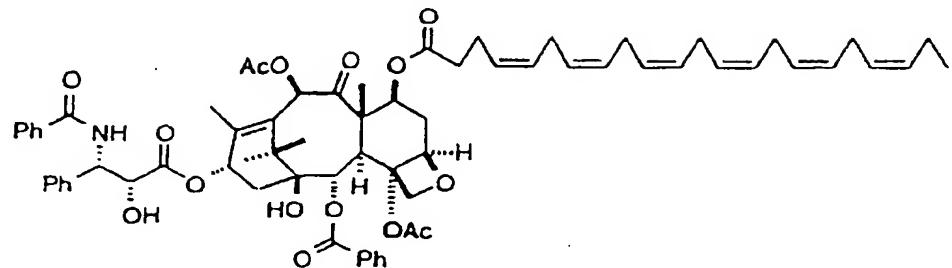
Those skilled in the art will be able to recognize with no more than routine experimentation numerous equivalents to the specific products and processes described above. Such equivalents are intended to be included within the scope of the appended claims.

CLAIMS

1. A method for targeting a pharmaceutical agent to a noncentral nervous system tissue to treat a noncentral nervous system condition comprising:
  - 5 administering to a subject in need of such treatment a covalent conjugate of *cis*-docosahexaenoic acid and a pharmaceutical agent effective for treating said condition.
- 10 2. The method of claim 1, wherein the *cis*-docosahexaenoic acid is conjugated directly to the pharmaceutical agent.
- 15 3. The method of claim 2, wherein the tissue is breast tissue and wherein the subject has a condition calling for treatment of breast tissue with the pharmaceutical agent.
4. The method of claim 2, wherein the tissue is gastrointestinal tissue and wherein the subject  
15 has a condition calling for treatment of gastrointestinal tissue with the pharmaceutical agent.
5. The method of claim 2, wherein the tissue is ovarian tissue and wherein the subject has a condition calling for treatment of ovarian tissue with the pharmaceutical agent.
- 20 6. The method of claim 2, wherein the pharmaceutical agent is a noncentral nervous system active agent that is nonactive within the central nervous system.
7. The method of claim 2, wherein the drug is an anti-cancer agent.
- 25 8. The method of claim 7, wherein the drug is Taxol.
9. The method of claim 8, wherein the conjugate is

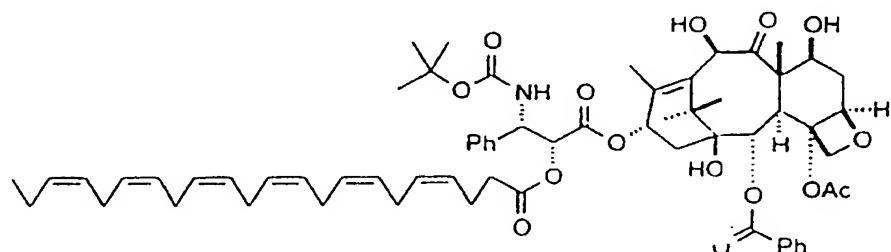


10. The method of claim 8, wherein the conjugate is

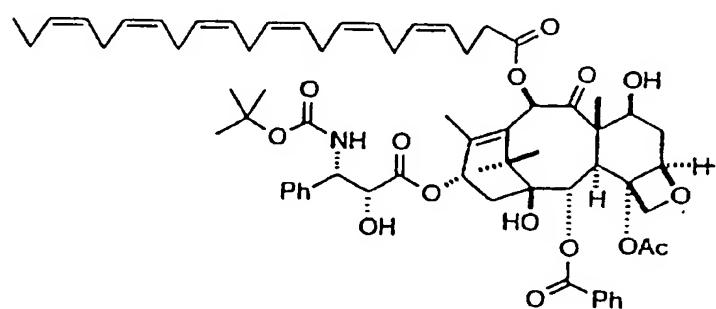


11. The method of claim 7, wherein the drug is Taxotere.

12. The method of claim 11, wherein the conjugate is

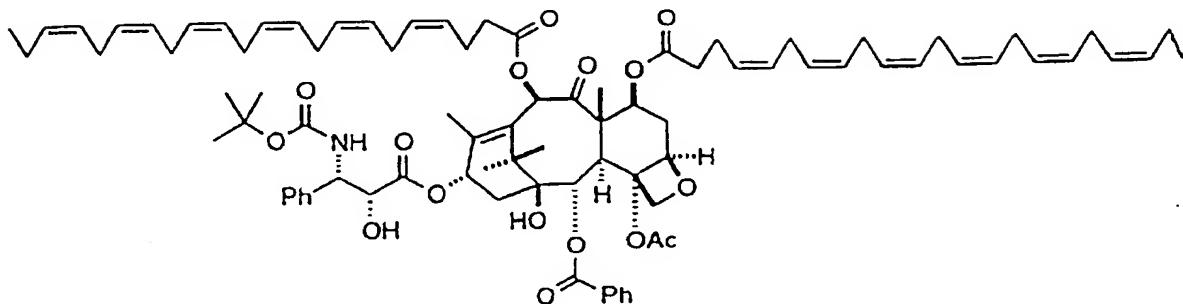


13. The method of claim 11, wherein the conjugate is

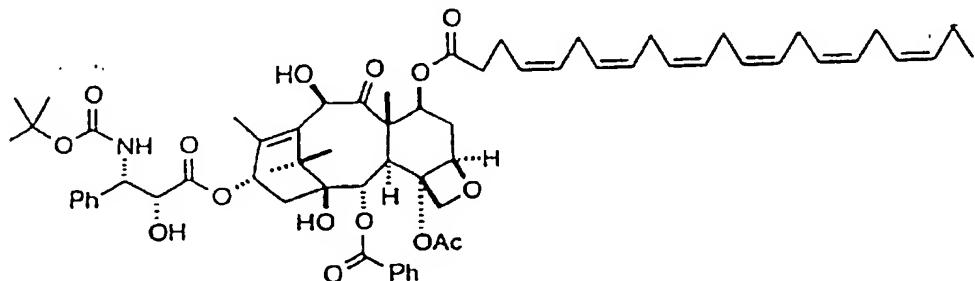


30

14. The method of claim 11, wherein the conjugate is



15. The method of claim 11, wherein the conjugate is



15 16. The method of claim 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein the condition is breast cancer.

20 17. The method of claim 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein the condition is colon cancer.

18. The method of claim 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein the condition is ovarian cancer.

25 19. A pharmaceutical preparation comprising:

a covalent conjugate of *cis*-docosahexaenoic acid and a noncentral nervous system active agent, and

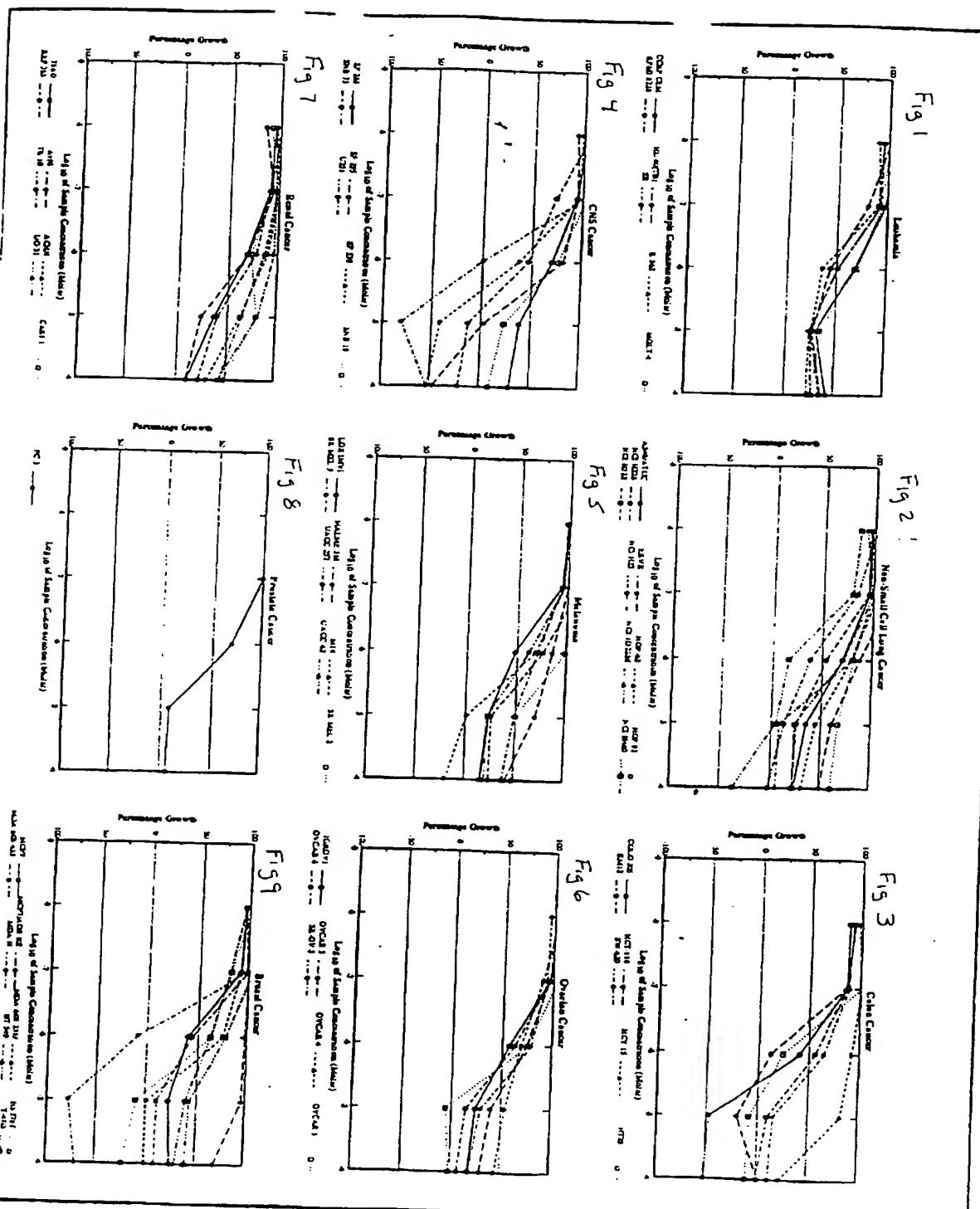
a pharmaceutically acceptable carrier.

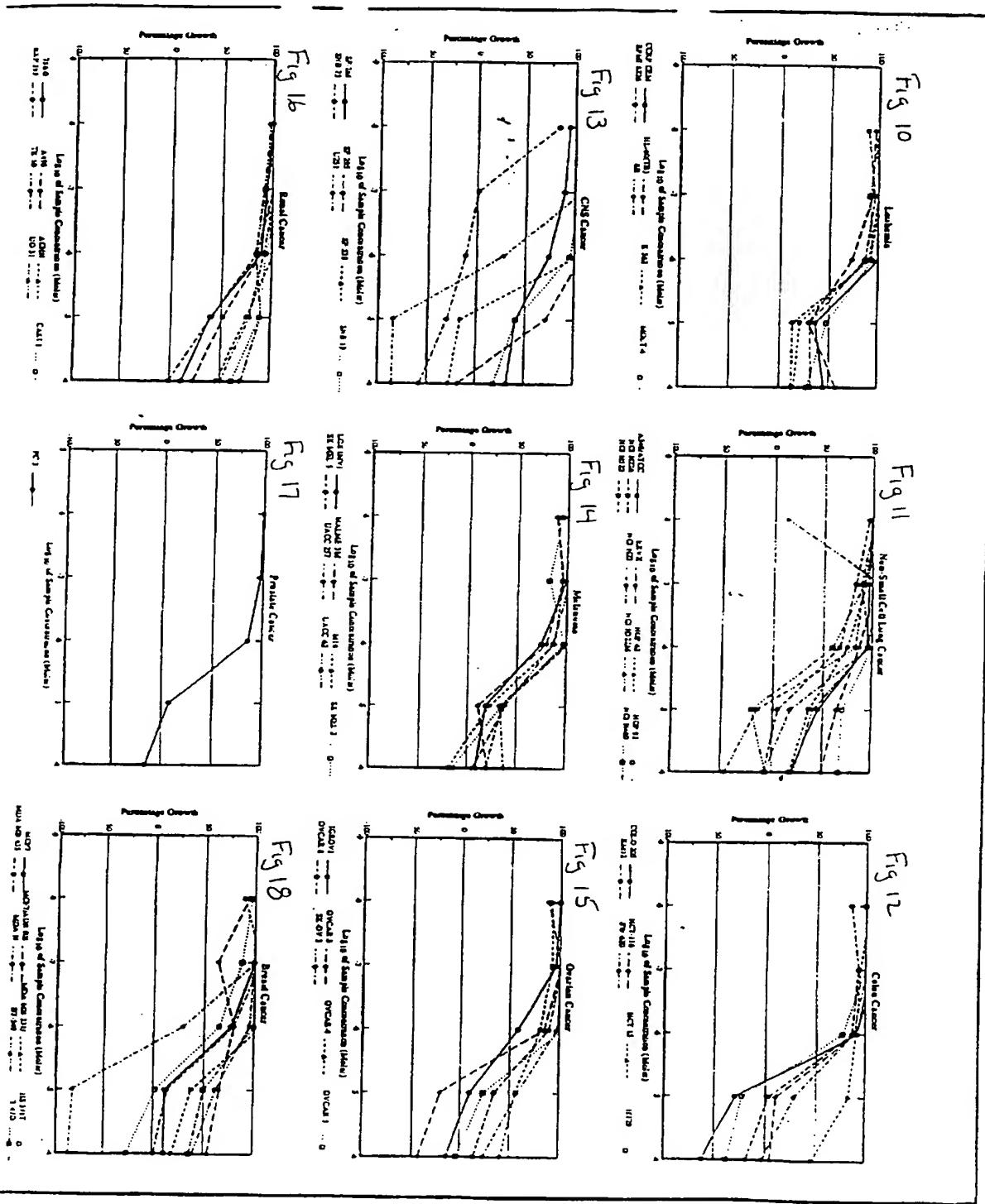
30 20. The pharmaceutical preparation of claim 19, wherein the *cis*-docosahexaenoic acid is conjugated directly to the active agent.

21. The pharmaceutical preparation as claimed in claim 20, wherein the noncentral nervous system active agent is active on a tissue selected from the group consisting of:

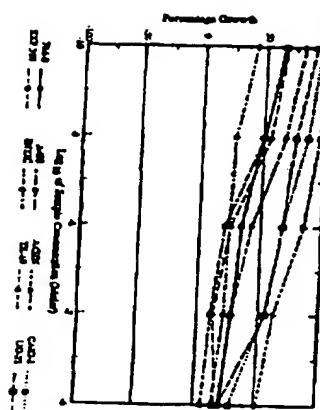
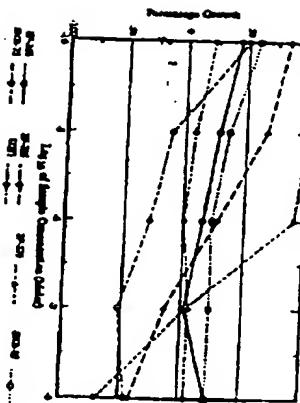
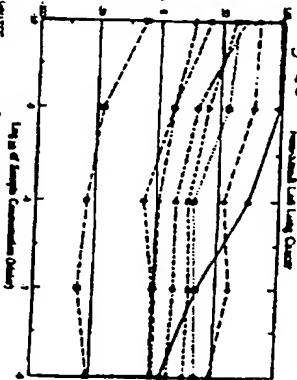
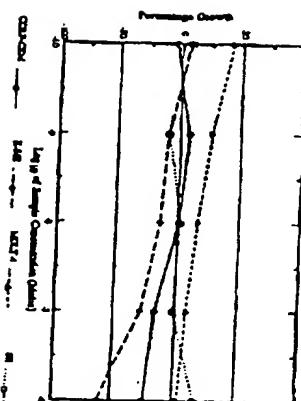
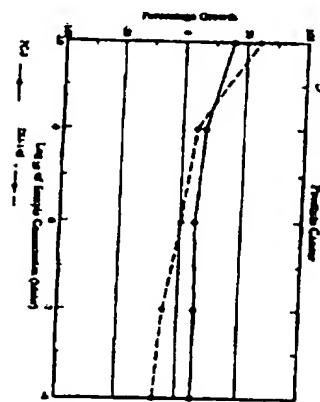
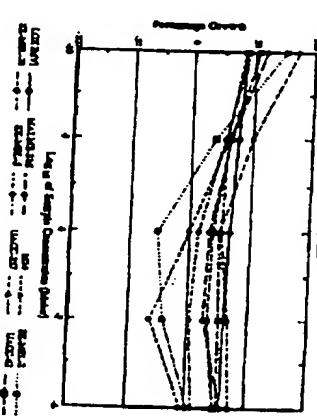
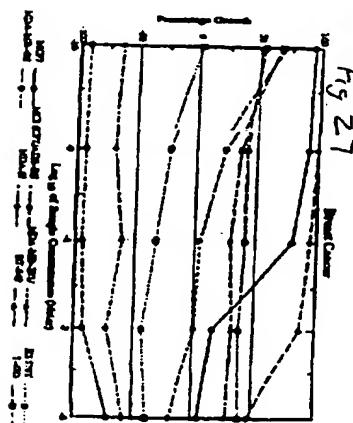
Blood and Blood Forming tissue; Cardiovascular system tissue; Digestive and excretory system tissue; Endocrine system tissue; Musclar system tissue; Reproductive System tissue; Respiratory system tissue; Skeletal system tissue; and Fiber and integumentary system tissue.

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Fig 25 *Initial Concentration*Fig 22 *Initial Concentration*Fig 23 *Initial Concentration*Fig 26 *Initial Concentration*Fig 24 *Initial Concentration*Fig 27 *Initial Concentration*



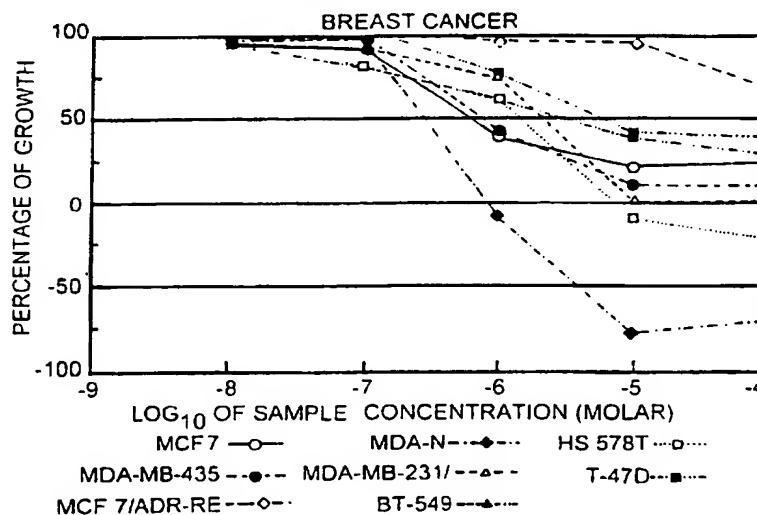
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(74) Agent: GATES, Edward, R.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).		

## (54) Title: DHA-PHARMACEUTICAL AGENT CONJUGATES

## (57) Abstract

The invention provides conjugates of *cis*-docosahexaenoic acid and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.



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# INTERNATIONAL SEARCH REPORT

Intell. Prop. Application No  
PCT/US 97/08867

**A. CLASSIFICATION OF SUBJECT MATTER**  
**IPC 6 A61K47/48**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**IPC 6 A61K**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 12530 A (BIOSIGNAL KUTATO FEJLESZTOE ;SYNTHETIC PEPTIDES INC (CA)) 9 June 1994 see page 25, line 8 - line 19; claims 1,3 ---	1-7, 16-21
E	WO 97 44026 A (NEUROMEDICA INC) 27 November 1997 see claims ---	1-21
E	WO 97 44336 A (NEUROMEDICA INC) 27 November 1997 see claims ---	1-21
X	WO 96 04001 A (MOLECULAR STRUCTURAL BIOTECHNO) 15 February 1996 see claims 1,6,8 ---	1-7, 16-21
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

18 December 1997

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 89 07938 A (SHASHOUA VICTOR E) 8 September 1989 see page 5, line 21 - line 22; claims ---	1,2,6, 19-21
P,A	WO 96 21658 A (LIPOSOME CO INC) 18 July 1996 see claims 1,24-26 ---	1-21
X	WO 92 20362 A (SHASHOUA VICTOR E) 26 November 1992 see page 21, line 22 - page 22, line 1; claims -----	1,2,6, 19-21

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/08867

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark:** Although claim(s) 1-18 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatinal Application No
PCT/US 97/08867

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 9220362 A	26-11-92	NONE	